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     (FILE 'HOME' ENTERED AT 14:03:59 ON 12 APR 2005)

     FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, WPIDS, SCISEARCH, AGRICOLA'
     ENTERED AT 14:04:20 ON 12 APR 2005
L1            80 S KAPLOW J?/AU
L2            15 S HAWS T?/AU
L3           217 S ROSIER M?/AU
L4           456 S DENEFLE P?/AU
L5           689 S L1-L4
L6         20500 S 14B
L7             1 S L6 AND L5
L8             1 S NFIF-14B
L9          1702 S NUCLEAR(5A)FACTOR (5A)KB
L10            7 S L9 (5A)INDUCING(5A)FACTOR?
L11        17367 S NUCLEAR(5A)FACTOR(5A)KAPPAB
L12          116 S L11 (5A)INDUCING(5A)FACTOR?
L13        50329 S NUCLEAR(5A)FACTOR(5A)KAPPA(5A)B
L14          330 S L13 (5A)INDUCING(5A)FACTOR?
L15            8 S NFIF?
L16            1 S L15 AND KAPPA
L17            1 S L15 AND 14B
L18            0 S L12 AND DNA (5A)(CODE? OR CODING OR ENCOD?)
L19            3 S (CODE? OR CODING OR ENCOD?) AND L12
L20           27 S (CODE? OR CODING OR ENCOD?) AND L14
L21            8 S GENE# (5A)L12
L22           34 S GENE# (5A)L14
L23            0 S (NUCLEIC OR DNA)(5A)L12
L24            1 S (NUCLEIC OR DNA)(5A)L14
L25           75 S L7 OR L8 OR L10 OR L15-L17 OR L19-L22 OR L24
L26           54 DUP REM L25 (21 DUPLICATES REMOVED)

=> d ibib abs l26 1-54

L26  ANSWER 1 OF 54  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:794545  HCAPLUS
DOCUMENT NUMBER:          141:289084
TITLE:                    Composition for inducing immunotolerance
INVENTOR(S):              Van Oosterhout, Antonius Josephus Maria; Kapsenberg,
                          Martien Lukas; Weller, Frank Reinoud; Taher, Yousef
                          Al-Madane; Lobato-Van Esch, Elisabeth Catharina
                          Adriana Maria; Vissers, Joost Lambert Max
PATENT ASSIGNEE(S):       Universiteit Utrecht Holding B.V., Neth.
SOURCE:                   Eur. Pat. Appl., 23 pp.
                          CODEN: EPXXDW
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     EP 1462111            A1    20040929    EP 2003-75909            20030328
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     WO 2004084927         A2    20041007    WO 2004-NL205            20040325
     WO 2004084927         A3    20050127
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2003-75909 A 20030328

AB The invention provides methods of treating allergic disorders and compns. for use therein. The methods comprise administering an allergen and one or more medicaments. These medicaments are compds. that inhibit the transcription of genes involved in the initiation of innate and specific immunity, thereby promoting the development of tolerance to these allergens, through inhibition of the NF-κB and/or the MAPK/AP-1 signal transduction pathway(s). In another embodiment, the use of DNA vaccines is disclosed that incorporate a gene **encoding** one or more allergen sequences or fragments thereof, in combination with genes **encoding** proteins that inhibit the activation of the NF-κB and/or the MAPK/AP-1 pathway or in combination with small interfering RNA sequences or anti-sense sequences that inhibit the expression of NF-κB and/or AP-1 proteins.

L26 ANSWER 2 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:728022 HCAPLUS
DOCUMENT NUMBER: 141:275257
TITLE: Nuclear factor-inducing kinase plays a crucial role in osteopontin-induced MAPK/IκBα kinase-dependent nuclear factor κB-mediated promatrix metalloproteinase-9 activation
AUTHOR(S): Rangaswami, Hema; Bulbule, Anuradha; Kundu, Gopal C.
CORPORATE SOURCE: National Center for Cell Science, Pune, 411 007, India
SOURCE: Journal of Biological Chemistry (2004), 279(37), 38921-38935
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have recently demonstrated that osteopontin (OPN) induces nuclear factor κB (NFκB)-mediated promatrix metalloproteinase-2 activation through IκBα/IκBα kinase (IKK) signaling pathways. However, the mol. mechanism(s) by which OPN regulates promatrix metalloproteinase-9 (pro-MMP-9) activation, MMP-9-dependent cell motility, and tumor growth and the involvement of upstream kinases in regulation of these processes in murine melanoma cells are not well defined. Here we report that OPN induced αvβ3 integrin-mediated phosphorylation and activation of nuclear factor-inducing kinase (NIK) and enhanced the interaction between phosphorylated NIK and IKKα/β in B16F10 cells. Moreover, NIK was involved in OPN-induced phosphorylations of MEK-1 and ERK1/2 in these cells. OPN induced NIK-dependent NFκB activation through ERK/IKKα/β-mediated pathways. Furthermore OPN enhanced NIK-regulated urokinase-type plasminogen activator (uPA) secretion, uPA-dependent pro-MMP-9 activation, cell motility, and tumor growth. Wild type NIK, IKKα/β, and ERK1/2 enhanced and kinase-neg. NIK (mut NIK), dominant neg. IKKα/β (dn IKKα/β), and dn

ERK1/2 suppressed the OPN-induced NFκB activation, uPA secretion, pro-MMP-9 activation, cell motility, and chemoinvasion. Pretreatment of cells with anti-MMP-2 antibody along with anti-MMP-9 antibody drastically inhibited the OPN-induced cell migration and chemoinvasion, whereas cells pretreated with anti-MMP-2 antibody had no effect on OPN-induced pro-MMP-9 activation suggesting that OPN induces pro-MMP-2 and pro-MMP-9 activations through two distinct pathways. The level of active MMP-9 in the OPN-induced tumor was higher compared with control. To our knowledge, this is the first report that NIK plays a crucial role in OPN-induced NFκB activation, uPA secretion, and pro-MMP-9 activation through MAPK/IKKα/β-mediated pathways, and all of these ultimately control the cell motility, invasiveness, and tumor growth.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:120476 BIOSIS
DOCUMENT NUMBER: PREV200500116656
TITLE: Intestinal cryptopatch formation in mice requires lymphotoxin alpha and the lymphotoxin beta receptor.
AUTHOR(S): Taylor, Rebekah T.; Luegering, Andreas; Newell, Kenneth A.; Williams, Ifor R. [Reprint Author]
CORPORATE SOURCE: Sch MedDept Pathol and Lab Med, Emory Univ, Whitehead Bldg 105D,615 Michael St, Atlanta, GA, 30322, USA irwilli@emory.edu
SOURCE: Journal of Immunology, (December 15 2004) Vol. 173, No. 12, pp. 7183-7189. print.
ISSN: 0022-1767 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Mar 2005
Last Updated on STN: 23 Mar 2005

AB Interactions between lymphotoxin (LT)alpha1beta2 on inducer cells and the lymphotoxin beta receptor (LTbetaR) on stromal cells initiate development of lymph nodes and Peyer's patches. In this study, we assessed the contributions of LTalpha and LTbetaR to the development of cryptopatches (CP), aggregates of T cell precursors in the mouse small intestine. Mice genetically deficient in LTalpha or LTbetaR lacked CP. Bone marrow from LTalpha-deficient mice was unable to initiate development of CP or isolated lymphoid follicles (ILF) after transfer to CDbeta2-null mice lacking CP and ILF. However, LTalpha-deficient bone marrow-derived cells contributed to CP formed in CDbeta2-null mice receiving a mixture of wild-type and LTalpha-deficient bone marrow cells. Transfer of wild-type bone marrow into irradiated LTalpha-deficient mice resulted in reconstitution of both CP and ILF. However, the LT-dependent formation of CP was distinguished from the LT-dependent formation of ILF and Peyer's patches by not requiring the presence of an intact NF-kappaB-inducing kinase gene. CP but not ILF were present in the small intestine from NF-kappaB-inducing kinase-deficient alymphoplasia mice, indicating that the alternate NF-kappaB activation pathway required for other types of LTbetaR-dependent lymphoid organogenesis is dispensable for CP development. In addition, we identified VCAM-1+ cells within both CP and ILF that are candidates for the stromal cells involved in receiving LT-dependent signals from the hemopoietic precursors recruited to CP. These findings demonstrate that interactions between cells expressing LTalpha1beta2 and LTbetaR are a shared feature in the development of all small intestinal lymphoid aggregates.

L26 ANSWER 4 OF 54 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2004225688 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15114132
TITLE: Tendon healing in vitro: activation of NIK, IKKalpha, IKKbeta, and NF- kappaB genes in signal pathway and proliferation of tenocytes.
AUTHOR: Tang Jin Bo; Xu Yan; Wang Xiao Tian
CORPORATE SOURCE: Hand Surgery Research Center, Department of Hand Surgery, Affiliated Hospital of Nantong Medical College, Nantong, Jiangsu, China.. jbtang@rics.bwh.harvard.edu
SOURCE: Plastic and reconstructive surgery, (2004 May) 113 (6) 1703-11.
Journal code: 1306050. ISSN: 0032-1052.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040506
Last Updated on STN: 20040526
Entered Medline: 20040525

AB Initiation of DNA transcription and proliferation of tendon cells are critical to tendon healing and require pivotal signals to the nucleus. Exploring intracellular signaling pathways pertinent to the healing process may reveal new approaches to accelerating the healing rate of the tendon. The authors investigated expression of NIK, IKKalpha, IKKbeta, and NF- kappaB genes in the signal pathway and tenocyte proliferation in an in vitro model in which cultured tenocytes were exposed to basic fibroblast growth factor (bFGF). Tenocytes were obtained from explant culture of rabbit intrasynovial tendons and were treated with bFGF at concentrations of 0, 2, or 10 ng/ml. Levels of expression of a series of **genes** for key **factors** along the signaling route--**nuclear factor** (NF)-**kappaB**-**inducing** kinase, inhibitor of kappa B kinase alpha and beta, and the NF-kappaB--were examined by quantitative analysis of products of reverse transcription and multiplex polymerase chain reactions. Proliferation of the cells was assessed with evaluation of growth curves and immunochemical labeling of the DNA of the cells. Expression levels of NIK, IKKalpha, IKKbeta, and NF-kappaB genes were significantly increased by bFGF at concentrations of 2 and 10 ng/ml. Western blot confirmed the increase of NF-kappaB in the tenocytes. The proliferation rate of the cells was significantly promoted by bFGF. Expression of these genes increased proportionately to the amounts of bFGF stimulating the cells and was correlated with increases in the proliferation rate. This study showed that expression of a series of genes along the NF-kappaB pathway was remarkably promoted by bFGF. The effects were proportionate to in vitro cell proliferation rate. Results of the study suggest that activation of a series of genes along the NF-kappaB pathway may play a pivotal role in initiating cell proliferation during the healing process of intrasynovial tendons. As activation of genes in signal transduction pathways is a new field in the biology of growth factor action with tremendous potential in promoting tissue repairs, manipulation of expression of a series of genes along the NF-kappaB pathway can be a new target of enhancing tendon healing through molecular mechanisms.

L26 ANSWER 5 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:505036 HCAPLUS
DOCUMENT NUMBER: 141:292763
TITLE: NF-κB inducing kinase activates NF-κB transcriptional activity independently of IκB

kinase γ through a p38 MAPK-dependent RelA phosphorylation pathway
AUTHOR(S): Jijon, H.; Allard, B.; Jobin, C.
CORPORATE SOURCE: Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC, 27599-7080, USA
SOURCE: Cellular Signalling (2004), 16(9), 1023-1032
CODEN: CESIEY; ISSN: 0898-6568
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mol. and biochem. anal. indicates that nuclear transcription factor κB (NF-κB)-inducing kinase (NIK) mediates IKK activation and NF-κB transcriptional activity. However, gene deletion studies suggest that NIK triggers gene expression without affecting IκBα degradation and NF-κB DNA binding activity. In order to investigate the role of NIK in NF-κB transcriptional activity, we used mouse embryonic fibroblasts (MEF) derived from wild-type (wt) and IκB kinase γ (IKKγ) gene-deficient (IKKγ-/-) mice. We report that although TNF-induced NF-κB transcriptional activity is abolished in IKKγ-/- cells, adenoviral gene delivery of NIK (Ad5NIK) still enhanced transcriptional activity and IL-6 mRNA accumulation. Moreover, NIK targets the transactivation function of NF-κB through stimulation of the transactivation domain (TAD) of RelA (S536) in IKKγ-/- cells. Interestingly, Ad5NIK, but not TNF, induces RelA S536 and p38 mitogen-activated protein kinase (MAPK) phosphorylation in IKKγ-/- cells. Functional anal. demonstrated that Ad5NIK-induced NF-κB transcriptional activity, IL-6 mRNA expression and RelA phosphorylation are inhibited by the p38 inhibitor SB203580, suggesting a role for this MAPK in NIK signaling to NF-κB. These data demonstrate for the first time the presence of an IKKγ-independent NIK/p38 MAPK-dependent signaling pathway that activates NF-κB and induces pro-inflammatory gene expression through RelA phosphorylation.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 6 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:324413 HCAPLUS
DOCUMENT NUMBER: 141:155995
TITLE: NF-κB-inducing kinase restores defective IκB kinase activity and NF-κB signaling in intestinal epithelial cells
AUTHOR(S): Russo, Maria Pia; Schwabe, Robert F.; Sartor, R. Balfour; Jobin, Christian
CORPORATE SOURCE: Medical Biomolecular Research Building, CB #7032, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7080, USA
SOURCE: Cellular Signalling (2004), 16(6), 741-750
CODEN: CESIEY; ISSN: 0898-6568
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cytokine-stimulated IκBα degradation is impaired in HT-29 and primary intestinal epithelial cells. To gain more insight into the mechanism of this defect, the authors dissected cytokine-induced NF-κB signaling pathway in HT-29 cells. IL-1β and TNF, alone

or in combination with IFNγ, failed to induce IκBα or IκBβ degradation in HT-29 cells. Despite similar 125I-IL-1β binding, HT-29 cells displayed no IRAK degradation, a 75% reduction of IKK activity, and decreased IκBα phosphorylation, NF-κB DNA binding activity, and IL-8 mRNA accumulation in response to IL-1β compared to Caco-2 cells. Selective activation of NF-κB pathway by adenoviral delivery of NF-κB-inducing kinase (Ad5NIK) or IKKβ (Ad5IKKβ) strongly activated IKK activity (>20 fold) in HT-29 cells with concomitant endogenous IκBα serine 32 phosphorylation and total IκBα degradation In addition, NF-κB DNA binding activity and IL-8 secretion is higher in Ad5NIK-infected than in IL-1β-stimulated HT-29 cells. Thus, altered NF-κB signaling is associated with impaired stimulation of an upstream IKK activator.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 7 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:988358 HCAPLUS
DOCUMENT NUMBER: 142:22250
TITLE: Receptor-specific signaling for both the alternative and the canonical NF-κB activation pathways by NF-κB-inducing kinase
AUTHOR(S): Ramakrishnan, Parameswaran; Wang, Wangxia; Wallach, David
CORPORATE SOURCE: Department of Biological Chemistry, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Immunity (2004), 21(4), 477-489
CODEN: IUNIEH; ISSN: 1074-7613
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The NF-κB-inducing kinase (NIK) induces proteolytic processing of NF-κB2/p100 and, hence, the generation of NF-κB dimers such as p52:RelB but was suggested not to signal for the processing of IκB. Here, we show that although the induction of IκB degradation in lymphocytes by TNF is independent of NIK, its induction by CD70, CD40 ligand, and BLyS/BAFF, which all also induce NF-κB2/p100 processing, does depend on NIK function. Both CD70 and TNF induce recruitment of the IKK kinase complex to their receptors. In the case of CD70, but not TNF, this process is associated with NIK recruitment and is followed by prolonged receptor association of just IKK1 and NIK. Recruitment of the IKK complex to CD27, but not that of NIK, depends on NIK kinase function. Our findings indicate that NIK participates in a unique set of proximal signaling events initiated by specific inducers, which activate both canonical and noncanonical NF-κB dimers.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 8 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:364450 HCAPLUS
TITLE: Preface - **NFIF** 2003
AUTHOR(S): Anon.
SOURCE: Trends in Food Science & Technology (2004), 15(7-8), 329
CODEN: TFTEEH; ISSN: 0924-2244
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; Miscellaneous
LANGUAGE: English
AB Unavailable

L26 ANSWER 9 OF 54 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:566864 SCISEARCH
THE GENUINE ARTICLE: 828HN
TITLE: **NFIF** 2003 - Preface
AUTHOR: ANON
SOURCE: TRENDS IN FOOD SCIENCE & TECHNOLOGY, (JUL-AUG 2004) Vol. 15, No. 7-8, pp. 329-329.
Publisher: ELSEVIER SCIENCE LONDON, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
ISSN: 0924-2244.
DOCUMENT TYPE: Editorial; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L26 ANSWER 10 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:285314 HCAPLUS
DOCUMENT NUMBER: 140:319509
TITLE: Role of protein kinase R in double-stranded RNA-induced expression of nitric oxide synthase in human astroglia
AUTHOR(S): Auch, Corey J.; Saha, Ramendra N.; Sheikh, Faruk G.; Liu, Xiaojuan; Jacobs, Bertram L.; Pahan, Kalipada
CORPORATE SOURCE: Department of Oral Biology, University of Nebraska Medical Center, Lincoln, NE, 68583-0740, USA
SOURCE: FEBS Letters (2004), 563(1-3), 223-228
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Environmental factor(s), such as viral infection, has been implicated as one of the triggering events leading to neuroinflammation in multiple sclerosis. This study underlines the importance of double-stranded RNA (dsRNA), the active component of a viral infection, in inducing the expression of inducible nitric oxide synthase (iNOS) in human astroglia. DsRNA in the form of synthetic polyinosinic-polycytidylic acid (poly IC) induced expression of iNOS and iNOS promoter-driven luciferase activity through activation of nuclear factor (NF)-κB and CCAAT/enhancer-binding proteinβ (C/EBPβ). In addition, we show that inhibitors of protein kinase R attenuated iNOS by suppressing the activation of NF-κB but not C/EBPβ. In contrast, knock down of p38 mitogen-activated protein kinase (MAPK) attenuated iNOS by suppressing the activation of C/EBPβ but not NF-κB. This study delineates a novel role of dsRNA in inducing the expression of iNOS through dsRNA-activated protein kinase (PKR)-mediated activation of NF-κB and p38-mediated activation of C/EBPβ in human astroglia that may participate in virus-induced neurol. abnormalities.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 11 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:459612 HCAPLUS
DOCUMENT NUMBER: 142:32532
TITLE: Inhibition of nuclear factor-κB and nitric oxide by curcumin induces G2/M cell cycle arrest and apoptosis in human melanoma cells
AUTHOR(S): Zheng, Mingzhong; Ekmekcioglu, Suhendan; Walch, Eugene T.; Tang, Chi-Hui; Grimm, Elizabeth A.

CORPORATE SOURCE: Department of Bioimmunotherapy, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Melanoma Research (2004), 14(3), 165-171
CODEN: MREEEH; ISSN: 0960-8931
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Curcumin (diferuloylmethane) inhibits tumor cell growth by inducing apoptosis in many tumor types, including melanoma, via complex and ill-defined pathways. Recent studies have shown that curcumin is both a nitric oxide scavenger and an inhibitor of inducible nitric oxide synthase (iNOS) expression, low levels of which correlate with antiapoptotic function and poor survival and which may be regulated by inhibition of nuclear factor-κB (NFκB) activation. To elucidate the mechanisms by which curcumin inhibits melanoma proliferation, we tested the in vitro effects of curcumin on specific cell cycle pathways and melanoma cell survival, including NFκB activation. Curcumin induced melanoma cell apoptosis and cell cycle arrest, which is associated with the down-regulation of NFκB activation, iNOS and DNA-dependent protein kinase catalytic subunit expression, and up-regulation of p53, p21, p27 and checkpoint kinase 2. Curcumin also down-regulated constitutive iNOS activity in melanoma cells. Our results demonstrate that curcumin arrested cell growth at the G2/M phase and induced apoptosis in human melanoma cells by inhibiting NFκB activation and thus depletion of endogenous nitric oxide. Therefore, curcumin should be considered further as a potential therapy for patients with melanoma.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 12 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:149456 HCAPLUS
TITLE: **NFIF** 2003
AUTHOR(S): Anon.
SOURCE: Trends in Food Science & Technology (2004), 15(3-4), 114
CODEN: TFTEEH; ISSN: 0924-2244
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; Miscellaneous
LANGUAGE: English

AB Unavailable

L26 ANSWER 13 OF 54 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:351412 SCISEARCH
THE GENUINE ARTICLE: 808GP
TITLE: **NFIF** 2003 - Preface
AUTHOR: Knorr D
SOURCE: TRENDS IN FOOD SCIENCE & TECHNOLOGY, (MAR 2004) Vol. 15, No. 3-4, pp. 114-114.
Publisher: ELSEVIER SCIENCE LONDON, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
ISSN: 0924-2244.
DOCUMENT TYPE: Editorial; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L26 ANSWER 14 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:717494 HCAPLUS

DOCUMENT NUMBER: 139:225545
TITLE: Human death domain containing receptors, their expression and therapeutic use thereof
INVENTOR(S): Yu, Guo-Liang; Ni, Jian; Gentz, Reiner L.; Dillon, Patrick J.
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 108 pp., Cont.-in-part of U.S. Ser. No. 557,908.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2003170203 | A1 | 20030911 | US 2002-189189 | | 20020705 |
| US 6153402 | A | 20001128 | US 1997-815469 | | 19970311 |
| US 2003077694 | A1 | 20030424 | US 1999-314889 | | 19990519 |
| US 2002009773 | A1 | 20020124 | US 1999-333966 | | 19990616 |
| US 6759513 | B2 | 20040706 | | | |
| US 6713061 | B1 | 20040330 | US 2000-557908 | | 20000421 |
| PRIORITY APPLN. INFO.: | | | US 1996-13285P | P | 19960312 |
| | | | US 1996-28711P | P | 19961017 |
| | | | US 1997-37341P | P | 19970206 |
| | | | US 1997-815469 | A2 | 19970311 |
| | | | US 1999-130488P | P | 19990422 |
| | | | US 1999-136741P | P | 19990528 |
| | | | US 2000-557908 | A2 | 20000421 |
| | | | US 2001-303155P | P | 20010706 |
| | | | US 2001-314314P | P | 20010824 |

AB The present invention relates to novel Death Domain Containing Receptor (DR3 and DR3-V1) proteins that are members of the tumor necrosis factor (TNF) receptor family. In particular, isolated nucleic acid mols. are provided **encoding** the human DR3 and DR3-V1 proteins. DR3 and DR3-V1 polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of DR3 and DR3-V1 activity.

L26 ANSWER 15 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-845333 [78] WPIDS
CROSS REFERENCE: 2003-845330 [78]
DOC. NO. CPI: C2003-237596
TITLE: New nuclear factor inducing kinase or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, useful for treating an autoimmune disease, infarct, Alzheimer's disease or atherosclerosis.
DERWENT CLASS: B04 D16
INVENTOR(S): RAMAKRISHNAN, P; SHMUSHKOVICH, T; WALLACH, D
PATENT ASSIGNEE(S): (YEDA) YEDA RES & DEV CO LTD
COUNTRY COUNT: 104
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2003087380 | A1 | 20031023 | (200378)* | EN | 98 |
| RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS | | | | | |

LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL
PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU
ZA ZM ZW
AU 2003226607 A1 20031027 (200436)
EP 1499729 A1 20050126 (200508) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV
MC MK NL PT RO SE SI SK TR

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2003087380 | A1 | WO 2003-IL317 | 20030415 |
| AU 2003226607 | A1 | AU 2003-226607 | 20030415 |
| EP 1499729 | A1 | EP 2003-746399 | 20030415 |
| | | WO 2003-IL317 | 20030415 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| AU 2003226607 | A1 Based on | WO 2003087380 |
| EP 1499729 | A1 Based on | WO 2003087380 |

PRIORITY APPLN. INFO: IL 2002-152183 20021008; IL 2002-149217 20020418

AN 2003-845333 [78] WPIDS
CR 2003-845330 [78]
AB WO2003087380 A UPAB: 20050202
NOVELTY - A NIK (**nuclear factor** (NF)-**kB-inducing** kinase) or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a DNA encoding NIK or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment;

(2) an antibody specific to the NIK or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment;

(3) a small molecule capable of modulating the interaction between interleukin 2 (IL-2) common gamma chain (c gamma c) and NIK kinase (NIKK), where the small molecule is obtainable by screening products of combinatorial chemistry in a luciferase system;

(4) treating a disease involving signaling of a cytokine through IL-2 c gamma c in the pathogenesis of the disease comprising administering the NIK or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, DNA, small molecule or antibody;

(5) a pharmaceutical composition comprising the NIK or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, DNA, small molecule and antibody;

(6) a polypeptide fragment of NIK, comprising the IL-2R c gamma c binding domain, or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or its fragment;

(7) a DNA encoding the polypeptide fragment of NIK;

(8) a vector comprising the DNA;

(9) a cell comprising the vector;

(10) producing NIK polypeptide comprising culturing the cell, and collecting the polypeptide produced; and

(11) an antibody, polyclonal or monoclonal, its chimeric antibody, fully humanized antibody, anti-anti-Id antibody, intrabody or its fragment that specifically recognizes and binds the polypeptide fragment of NIK.

ACTIVITY - Antiinflammatory; Gastrointestinal-Gen; Antiarthritic; Antirheumatic; Osteopathic; Antiasthmatic; Cardiant; Nootropic; Neuroprotective; Antiarteriosclerotic; Immunosuppressive; Antianemic; Antithyroid. No biological data given.

MECHANISM OF ACTION - Gene Therapy. No biological data given.

USE - The NIK or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, DNA, small molecule and antibody are useful for modulating the interaction between interleukin 2 (IL-2) common gamma chain (c gamma c) and NIK; and for the manufacture of a medicament for the treatment of a disease, e.g. a disease resulting from excessive immune response such as rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease or atherosclerosis; or an autoimmune disease such as immune thyroiditis, or other arthropaties, such as autoimmune hemolytic anemia. The small molecule is useful for modulating signaling through c gamma c (all claimed).

Dwg.0/16

L26 ANSWER 16 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-845330 [78] WPIDS

CROSS REFERENCE: 2003-845333 [78]

DOC. NO. CPI: C2003-237593

TITLE: New interleukin-2 common gamma chain or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment useful for treating Alzheimer's disease or atherosclerosis.

DERWENT CLASS: B04 D16

INVENTOR(S): RAMAKRISHNAN, P; SHMUSHKOVICH, T; WALLACH, D

PATENT ASSIGNEE(S): (YEDA) YEDA RES & DEV CO LTD

COUNTRY COUNT: 104

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2003087374 | A1 | 20031023 | (200378)* | EN | 103 |
| RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW | | | | | |
| AU 2003222415 | A1 | 20031027 | (200436) | | |
| EP 1499724 | A1 | 20050126 | (200508) | EN | |
| R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR | | | | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2003087374 | A1 | WO 2003-IL316 | 20030415 |
| AU 2003222415 | A1 | AU 2003-222415 | 20030415 |

| | | | |
|---|---|---|---|
| EP 1499724 | A1 | EP 2003-717504 | 20030415 |
| | | WO 2003-IL316 | 20030415 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| AU 2003222415 | A1 Based on | WO 2003087374 |
| EP 1499724 | A1 Based on | WO 2003087374 |

PRIORITY APPLN. INFO: IL 2002-152183 20021008; IL 2002-149217 20020418

AN 2003-845330 [78] WPIDS

CR 2003-845333 [78]

AB WO2003087374 A UPAB: 20050202

NOVELTY - An interleukin 2 (IL-2) common gamma chain (c gamma c) or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a DNA encoding c gamma c or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment;

(2) an antibody specific to the c gamma c or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment;

(3) a small molecule capable of modulating the interaction between IL-2 common gamma chain (c gamma c) and **nuclear factor kB inducing** kinase kinase (NIKK), where the small molecule is obtainable by screening products of combinatorial chemistry in a luciferase system;

(4) treating a disease involving the activity of NIK (**nuclear factor kB inducing** kinase) in the pathogenesis of the disease comprising administering the c gamma c or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, DNA, small molecule or antibody;

(5) a pharmaceutical composition comprising the c gamma c or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, DNA, small molecule and antibody;

(6) a polypeptide fragment of c gamma c, comprising the NIK binding domain, or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or its fragment;

(7) a DNA encoding the polypeptide fragment of NIK;

(8) a vector comprising the DNA;

(9) a cell comprising the vector;

(10) producing c gamma c polypeptide by culturing the cell, and collecting the polypeptide produced; and

(11) an antibody, polyclonal or monoclonal, its chimeric antibody, fully humanized antibody, anti-anti-Id antibody, intrabody or its fragment that specifically recognizes and binds the polypeptide fragment of NIK.

ACTIVITY - Antiinflammatory; Gastrointestinal-Gen.; Antiarthritic; Antirheumatic; Osteopathic; Antiasthmatic; Cardiant; Nootropic; Neuroprotective; Antiarteriosclerotic; Immunosuppressive; Antithyroid. No biological data given.

MECHANISM OF ACTION - Gene Therapy. No biological data given.

USE - The c gamma c or its mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment, DNA, small molecule and antibody are useful for modulating the interaction between IL-2 common gamma chain (c gamma c) and NIK; and for the manufacture of a medicament for the treatment of a disease, e.g. a disease resulting from excessive immune response such as rheumatoid arthritis,

osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease or atherosclerosis; or an autoimmune disease such as immune thyroiditis, or other arthropaties, e.g. autoimmune hemolytic anemia. The small molecule is useful for modulating signaling trough c gamma c (all claimed).
Dwg.0/16

L26 ANSWER 17 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:98629 BIOSIS
DOCUMENT NUMBER: PREV200400101680
TITLE: Molecular genetic analysis of human herpes virus 8-**encoded** viral FLICE inhibitory protein-induced NF-kappaB activation.
AUTHOR(S): Matta, Hittu; Sun, Qinmiao; Moses, Gregory; Chaudhary, Preet M. [Reprint Author]
CORPORATE SOURCE: Hamon Center for Therapeutic Oncology Research, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX, 75390-8593, USA
preet.chaudhary@utsouthwestern.edu
SOURCE: Journal of Biological Chemistry, (December 26 2003) Vol. 278, No. 52, pp. 52406-52411. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Feb 2004
Last Updated on STN: 18 Feb 2004

AB The human herpes virus 8 (HHV8)-**encoded** viral FLICE inhibitory protein (vFLIP), also known as K13, is known to activate the NF-kappaB pathway, a property not shared by other vFLIPs. Previous studies have demonstrated that HHV8 vFLIP K13 interacts with several cellular signaling proteins involved in NF-kappaB activation, such as receptor-interacting protein, NF-kappaB-inducing kinase, IkappaB kinase (IKK) 1, IKK2, and NF-kappaB essential modulator (NEMO). In this report we have used cell lines deficient in the above proteins to investigate the mechanism of NF-kappaB activation via HHV8 vFLIP K13. We demonstrate that receptor-interacting protein and NF-kappaB-inducing kinase are dispensable for vFLIP K13-induced NF-kappaB DNA binding and transcriptional activation. On the other hand, vFLIP K13-induced NF-kappaB DNA binding activity is significantly reduced, although not absent, in cells deficient in IKK1, IKK2, and NEMO. Furthermore, vFLIP K13-induced NF-kappaB transcriptional activity is only weakly present in IKK1-deficient cells and almost completely absent in those deficient in IKK2 and NEMO. HHV8 vFLIP K13-induced NF-kappaB activation in IKK1- and IKK2-deficient fibroblasts could be rescued by wild type but not by the kinase-inactive mutants of IKK1 and IKK2, respectively. Consistent with the above results, vFLIP K13-induced NF-kappaB activation could be effectively blocked by chemical inhibitors of the kinase activity of IKK1 and IKK2. Thus, a cooperative interaction of all three subunits of the IKK complex is required for maximal NF-kappaB activation via HHV8 vFLIP K13. Selective inhibitors of the IKK1 kinase activity may have a role in the treatment of disorders caused by abnormal NF-kappaB activation by HHV8 vFLIP K13.

L26 ANSWER 18 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:749174 HCAPLUS
DOCUMENT NUMBER: 139:349206
TITLE: Molecular mechanism of psychosine-induced cell death in human oligodendrocyte cell line

AUTHOR(S): Haq, Ehtishamul; Giri, Shailendra; Singh, Inderjit; Singh, Avtar K.
CORPORATE SOURCE: Department of Pediatrics, Medical University of South Carolina, USA
SOURCE: Journal of Neurochemistry (2003), 86(6), 1428-1440
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study delineates the mol. mechanism underlying psychosine-induced oligodendroglial cell death. An immortalized human oligodendroglial cell line, MO3.13, was treated with exogenous psychosine (β-galactosylsphingosine), a toxic metabolite that accumulates in the tissues of patients with Krabbe's disease. The mode of cell death induced by psychosine was found to be apoptotic, as revealed by different apoptotic markers viz., TUNEL, DNA fragmentation and caspase cleavage/activation. The action of psychosine was redox-sensitive, as measured by changes in mitochondrial membrane potential ($\psi\Delta$), and this effect of psychosine could be reversed by pre-treatment with the antioxidant mols. N-acetyl-L-cysteine or pro-cysteine. Psychosine directly affects the mitochondria as revealed by the activation of caspase 9 but not caspase 8. Up-regulation of the c-jun/c-jun N-terminal kinase pathway by psychosine leads to the induction of AP-1 and, at the same time, psychosine also down-regulates the lipopolysaccharide-induced NF-κB transactivation. These observations indicate that the mechanism of action of psychosine is, through the up-regulation of AP-1, a pro-apoptotic pathway as well as, through the down-regulation of the NF-κB pathway, an antiapoptotic pathway.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 19 OF 54 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003172306 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12671895
TITLE: Helicobacter pylori induces matrix metalloproteinase-9 through activation of nuclear factor kappaB.
AUTHOR: Mori Naoki; Sato Hiroshi; Hayashibara Toshihisa; Senba Masachika; Geleziunas Romas; Wada Akihiro; Hirayama Toshiya; Yamamoto Naoki
CORPORATE SOURCE: Department of Virology, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan.. n-mori@med.u-ryukyu.ac.jp
SOURCE: Gastroenterology, (2003 Apr) 124 (4) 983-92.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030416
Last Updated on STN: 20030502
Entered Medline: 20030501

AB BACKGROUND & AIMS: Matrix metalloproteinases (MMPs), enzymes capable of degrading extracellular matrix components, are believed to be active in connective tissue remodeling associated with various physiologic processes and in pathologic conditions. The aim of this study was to analyze the molecular mechanism responsible for Helicobacter pylori-mediated MMP expression. METHODS: Expression of MMP messenger RNA and MMP activity were assessed by reverse-transcription polymerase chain reaction and zymography, respectively. Chloramphenicol acetyltransferase assay was

used to monitor activation of the MMP-9 gene promoter, and electrophoretic mobility shift assay was used to explore the binding of transcription factors to this promoter. Gastric tissue samples were immunohistochemically stained for MMP-9. RESULTS: H. pylori induced MMP-9 expression in 2 gastric epithelial cell lines but had no effect on MMP-2. Induction of MMP-9 was dependent on an intact cag pathogenicity island. Activation of the MMP-9 promoter by H. pylori occurred through the action of nuclear factor kappaB. Transfection of kinase-deficient mutants of IkappaB kinase and nuclear factor kappaB-inducing kinase inhibited H. pylori-mediated activation of MMP-9. MMP-9 expression was higher in epithelial cells of H. pylori-positive tissue compared with those of H. pylori-negative tissue. CONCLUSIONS: H. pylori induced activation of nuclear factor kappaB through an intracellular signaling pathway that involved IkappaB kinase and **nuclear factor kappaB-inducing** kinase, leading to MMP-9 **gene** transcription. MMP-9 induction by H. pylori may play an important role in gastric inflammation, ulcer formation, and carcinogenesis.

L26 ANSWER 20 OF 54 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:378193 SCISEARCH
THE GENUINE ARTICLE: 671HV
TITLE: Topological requirements and signaling properties of T cell-activating, anti-CD28 antibody superagonists
AUTHOR: Luhder F; Huang Y; Dennehy K M; Guntermann C; Muller I; Winkler E; Kerkau T; Ikemizu S; Davis S J; Hanke T; Hunig T (Reprint)
CORPORATE SOURCE: Univ Wurzburg, Inst Virol & Immunobiol, Versbacher Str 7, D-97078 Wurzburg, Germany (Reprint); Univ Wurzburg, Inst Virol & Immunobiol, D-97078 Wurzburg, Germany; TeGenero Immuno Therapeut AG, D-97076 Wurzburg, Germany; Kumamoto Univ, Grad Sch Pharmaceut Sci, Div Struct Biol, Kumamoto 8620973, Japan; Univ Oxford, Nuffield Dept Med, Oxford OX3 9DU, England
COUNTRY OF AUTHOR: Germany; Japan; England
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (21 APR 2003) Vol. 197, No. 8, pp. 955-966.
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021 USA.
ISSN: 0022-1007.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 53

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Full activation of naive T cells requires both engagement of the T cell antigen receptor (TCR; signal 1) and costimulatory signaling by CD28 (signal 2). We previously identified two types of rat CD28-specific monoclonal antibodies (mAbs): "conventional," TCR signaling-dependent costimulatory mAbs and "superagonistic" mAbs capable of inducing the full activation of primary resting T cells in the absence of TCR ligation both in vitro and in vivo. Using chimeric rat/mouse CD28 molecules, we show that the superagonists bind exclusively to the laterally exposed C"D loop of the immunoglobulin-like domain of CD28 whereas conventional, costimulatory mAbs recognize an epitope close to the binding site for the natural CD80/CD86 ligands. Unexpectedly, the C"D loop reactivity of a panel of new antibodies raised against human CD28 could be predicted solely on the basis of their superagonistic properties. Moreover, mouse CD28 molecules engineered to express the rat or human C"D loop sequences activated T cell hybridomas without TCR ligation when cross-linked by

superagonistic mAbs. Finally, biochemical analysis revealed that superagonistic CD28 signaling activates the **nuclear factor KB** pathway without **inducing** phosphorylation of either TCRzeta or ZAP70. Our findings indicate that the topologically constrained interactions of anti-CD28 superagonists bypass the requirement for signal 1 in T cell activation. Antibodies with this property may prove useful for the development of T cell stimulatory drugs.

L26 ANSWER 21 OF 54 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003364847 EMBASE
TITLE: Thymic medullary epithelial cell differentiation, thymocyte emigration, and the control of autoimmunity require lympho-epithelial cross talk via LTβR.
AUTHOR: Boehm T.; Scheu S.; Pfeffer K.; Bleul C.C.
CORPORATE SOURCE: C.C. Bleul, Max Planck Inst. for Immunobiology, Stuebeweg 51, 79108 Freiburg, Germany. bleul@immunbio.mpg.de
SOURCE: Journal of Experimental Medicine, (1 Sep 2003) Vol. 198, No. 5, pp. 757-769.
Refs: 43
ISSN: 0022-1007 CODEN: JEMEAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030925
Last Updated on STN: 20030925

AB Thymocytes depend on the interaction with thymic epithelial cells for the generation of a diverse, nonautoreactive T cell repertoire. In turn, thymic epithelial cells acquire their three-dimensional cellular-organization via instructive signals from developing thymocytes. The nature of these signals has been elusive so far. We show that thymocytes and medullary epithelial cells (MECs) communicate via the lymphotoxin β receptor (LTβR) signaling axis. Normal differentiation of thymic MECs requires LTβR ligand on thymocytes and LTβR together with **nuclear factor-KB-inducing** kinase (Nik) in thymic epithelial cells. Impaired lympho-epithelial cross talk in the absence of the LTβR causes aberrant differentiation and reduced numbers of thymic MECs, leads to the retention of mature T lymphocytes, and is associated with autoimmune phenomena, suggesting an unexpected role for LTβR signaling in central tolerance induction.

L26 ANSWER 22 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:455341 HCAPLUS
DOCUMENT NUMBER: 139:228793
TITLE: Essential role of NF-κB-inducing kinase in T cell activation through the TCR/CD3 pathway
AUTHOR(S): Matsumoto, Mitsuru
CORPORATE SOURCE: Division of Molecular Immunology, Institute for Enzyme Research, University of Tokushima, Tokushima, 770-8503, Japan
SOURCE: Rinsho Men'eki (2003), 39(3), 344-348
CODEN: RNMKAU; ISSN: 0386-9695
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review. The topics discussed are (1) impaired T cell activation and interleukin-2 production caused by impaired NF-κB activity in NIK mutant aly mice; (2) NIK-independent costimulatory signal pathways of T cells in aly mice; (3) regulation of T cell activation by NIK and protein kinase C-Θ (PKC-Θ); and (4) involvement of NIK and PKC-Θ in NF-κB activation pathways downstream of TCR/CD3.

L26 ANSWER 23 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:398478 BIOSIS
DOCUMENT NUMBER: PREV200300398478
TITLE: Silica induces nuclear factor-kappaB activation through TAK1 and NIK in Rat2 cell line.
AUTHOR(S): Cho, HyeYoung; Lee, Jooyong; Kwak, Noh-Jin; Lee, Kweon-Haeng; Rha, SukJoo; Kim, Young-Hoon; Cho, Yong-Yeun; Yang, Ki-Hwa; Kim, KyoungAh; Lim, Young [Reprint Author]
CORPORATE SOURCE: Department of Occupational and Environmental Medicine, St. Mary's Hospital, The Catholic University of Korea, 62 Youdo-dong, Youngdunpo-gu, Seoul, 150-010, South Korea nglim@catholic.ac.kr
SOURCE: Toxicology Letters (Shannon), (August 28 2003) Vol. 143, No. 3, pp. 323-330. print.
CODEN: TOLED5. ISSN: 0378-4274.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Aug 2003
Last Updated on STN: 27 Aug 2003

AB Silica has been known to be a factor in acute cell injury and chronic pulmonary fibrosis. In Rat2 fibroblasts, silica induced the activation of nuclear factor-kappa B (NF-kappaB), which plays a crucial role in regulating the expression of many genes involved in the subsequent inflammatory response. In addition, we observed that transforming growth factor-beta activated kinase 1 (TAK1) and NF-kappaB-inducing kinase (NIK) were involved in silica-mediated NF-kappaB activation in Rat2 cells. The dominant negative mutant forms of TAK1 and NIK inhibited the silica-induced NF-kappaB activation in Rat2 cells. Furthermore, we demonstrated that endogenous TAK1 is phosphorylated in silica-stimulated Rat2 cells. These results indicate that TAK1 functions as a critical mediator in the silica-induced signaling pathway.

L26 ANSWER 24 OF 54 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2003179889 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12668260
TITLE: Mutational study of the **nuclear factor kappa B inducing** kinase **gene** in patients with progressive supranuclear palsy.
AUTHOR: Campdelacreu Jaume; Ezquerra Mario; Munoz Esteban; Oliva Rafael; Tolosa Eduardo
CORPORATE SOURCE: Parkinson's Disease and Movement Disorders Unit, Neurology Service, Institut Clinic de Malalties del Sistema Nervios, Hospital Clinic Universitari, Villarroel 170, 08036 Barcelona, Spain.
SOURCE: Neuroscience letters, (2003 Apr 10) 340 (2) 158-60.
Journal code: 7600130. ISSN: 0304-3940.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030418
Last Updated on STN: 20030530
Entered Medline: 20030529

AB The **nuclear factor kappa B** **inducing** kinase **gene** (NIK) is located near the region of the haplotype associated with progressive supranuclear palsy (PSP) in chromosome 17q. We have analysed the **coding** region of the NIK gene in PSP patients through single strand conformation polymorphism and direct sequencing, in order to investigate the possible existence of pathogenic mutations. A change in exon 15 consisting of a G/C variation in position 2839 was found. This change was then analysed through restriction endonuclease HphI in 40 PSP samples and 35 control samples, but no differences in allelic frequency were found between the PSP and control groups. Our results do not support a pathogenic role of the NIK gene in PSP.


L26 ANSWER 25 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:179809 BIOSIS
DOCUMENT NUMBER: PREV200300179809
TITLE: RelB is required for Peyer's patch development: Differential regulation of p52-RelB by lymphotoxin and TNF.
AUTHOR(S): Yilmaz, Z. Buket; Weih, Debra S.; Sivakumar, Vallabhapurapu; Weih, Falk [Reprint Author]
CORPORATE SOURCE: Forschungszentrum Karlsruhe, Institute of Toxicology and Genetics, D-76021, Karlsruhe, Germany
falk.weih@itg.fzk.de
SOURCE: EMBO (European Molecular Biology Organization) Journal, (January 2 2003) Vol. 22, No. 1, pp. 121-130. print.
ISSN: 0261-4189 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Apr 2003
Last Updated on STN: 9 Apr 2003

AB Targeted disruption of the Rel/NF-kappaB family members NF-kappaB2, **encoding** p100/p52, and RelB in mice results in anatomical defects of secondary lymphoid tissues. Here, we report that development of Peyer's patch (PP)-organizing centers is impaired in both NF-kappaB2- and RelB-deficient animals. IL-7-induced expression of lymphotoxin (LT) in intestinal cells, a crucial step in PP development, is not impaired in RelB-deficient embryos. LTbeta receptor (LTbetaR)-deficient mice also lack PPs, and we demonstrate that LTbetaR signaling induces p52-RelB and classical p50-RelA heterodimers, while tumor necrosis factor (TNF) activates only RelA. LTbetaR-induced binding of p52-RelB requires the degradation of the inhibitory p52 precursor, p100, which is mediated by the NF-kappaB-inducing kinase (NIK) and the IkappaB kinase (IKK) complex subunit IKKalpha, but not IKKbeta or IKKgamma. Activation of RelA requires all three IKK subunits, but is independent of NIK. Finally, we show that TNF increases p100 levels, resulting in the specific inhibition of RelB DNA binding via the C-terminus of p100. Our data indicate an important role of p52-RelB heterodimers in lymphoid organ development downstream of LTbetaR, NIK and IKKalpha.

L26 ANSWER 26 OF 54 MEDLINE on STN
ACCESSION NUMBER: 2003414301 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12953803
TITLE: Survival and proliferation factors of normal and malignant

plasma cells.

AUTHOR: Klein Bernard; Tarte Karin; Jourdan Michel; Mathouk Karene; Moreaux Jerome; Jourdan Eric; Legouffe Eric; De Vos John; Rossi Jean Francois

CORPORATE SOURCE: INSERM U475 and Unit for Cellular and Gene Therapy, CHU Montpellier, Montpellier, France.. klein@montp.inserm.fr

SOURCE: International journal of hematology, (2003 Aug) 78 (2) 106-13. Ref: 81
Journal code: 9111627. ISSN: 0925-5710.

PUB. COUNTRY: Ireland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310

ENTRY DATE: Entered STN: 20030905
Last Updated on STN: 20031021
Entered Medline: 20031020

AB Since the first identification of interleukin (IL)-6 as a myeloma cell growth factor by Dr. Kawano's and Dr. Klein's groups 14 years ago, numerous studies have emphasized its major roles in the emergence of malignant plasma cells in vivo and in the generation of normal plasma cells. Four transcription factors control B-cell differentiation into plasma cells. The B-cell transcription factor pax-5 is mainly responsible for a B-cell phenotype, and bcl-6 represses the plasma cell transcription factor blimp-1 and plasma cell differentiation. bcl-6 expression is triggered by CD40 and IL-4 activation. A lack of CD40 and IL-4 activation yields a down-regulation of bcl-6 expression, and IL-6 stimulation yields an up-regulation of blimp-1, mainly through STAT3 activation. Blimp-1 further down-regulates bcl-6 and pax-5 expression and makes plasma cell differentiation possible. IL-6 as well as IL-10 up-regulate XBP-1. XBP-1 is another transcription factor that is involved in plasma cell differentiation and whose gene expression is shut down by pax-5. The plasma cell transcription factors blimp-1 and XBP-1 are up-regulated, and the B-cell transcription factors bcl-6 and pax-5 are down-regulated, in malignant cells compared to B-cells. Apart from the recent identification of these 4 transcription factors, the factors involved in normal plasma cell generation are mostly unknown. Regarding malignant plasma cells, 3 categories of growth factors have been identified: (1) the IL-6 family cytokines, IL-10, and interferon alpha that activate the Janus kinase-signal transducer and activator of transcription (JAK/STAT) and mitogen-activated protein (MAP) kinase pathways; (2) growth factors activating the phosphatidylinositol (PI)-3 kinase/AKT and MAP kinase pathways, unlike the JAK/STAT pathway (insulin-like growth factor 1, hepatocyte growth factor, and members of the epidermal growth factor family able to bind syndecan-1 proteoglycan); and (3) B-cell-activating **factor** (BAFF) or proliferation-**inducing** ligand (APRIL) that activate the **nuclear factor KB** and PI-3 kinase/AKT pathways. BAFF and APRIL bind to BAFF receptor and TACI and are major B-cell survival factors. Recent data indicate that these various growth factors may cooperate to provide optimum signaling because they are localized together and with cytoplasmic transduction elements in caveolinlinked membrane caveolae. The identification of these myeloma cell growth factors and of the associated transduction pathways should provide novel therapeutic targets in multiple myeloma.

L26 ANSWER 27 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-471256 [50] WPIDS
DOC. NO. CPI: C2002-133946

TITLE: Novel isolated PAAD domain containing polypeptide useful for **inducing** apoptosis by inhibiting **nuclear factor kappa** **B** activation and in **gene** therapy for treating cancer.

DERWENT CLASS: B04 D16

INVENTOR(S): ARIZA, M E; CHU, Z; FIORENTINO, L; GODZIK, A; PAWLOWSKI, K; REED, J C; STEHLIK, C

PATENT ASSIGNEE(S): (BURN-N) BURNHAM INST; (ARIZ-I) ARIZA M E; (CHUZ-I) CHU Z; (FIOR-I) FIORENTINO L; (GODZ-I) GODZIK A; (PAWL-I) PAWLOWSKI K; (REED-I) REED J C; (STEH-I) STEHLIK C

COUNTRY COUNT: 97

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2002026780 | A2 | 20020404 | (200250)* | EN | 145 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW | | | | | |
| AU 2001096333 | A | 20020408 | (200252) | | |
| US 2003077699 | A1 | 20030424 | (200353)# | | 93 |
| US 2004142374 | A1 | 20040722 | (200449)# | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2002026780 | A2 | WO 2001-US30160 | 20010926 |
| AU 2001096333 | A | AU 2001-96333 | 20010926 |
| US 2003077699 | A1 Provisional | US 2000-367367P | 20000926 |
| | | US 2001-965621 | 20010925 |
| US 2004142374 | A1 Provisional | US 2000-367367P | 20000926 |
| | Cont of | US 2001-965621 | 20010925 |
| | | US 2004-781294 | 20040217 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| AU 2001096333 | A Based on | WO 2002026780 |

PRIORITY APPLN. INFO: US 2000-671760 20000926; US 2001-965621 20010925; US 2004-781294 20040217

AN 2002-471256 [50] WPIDS

AB WO 200226780 A UPAB: 20031120

NOVELTY - Isolated PAAD domain containing polypeptide (I) comprising 80% identity to the amino acid sequence (S1) of PAAD and nucleotide binding protein (PAN) 2-6, pyrin 2, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC)-2 fully defined in specification, where (I) is biologically active, is new.

DETAILED DESCRIPTION - An isolated PAAD (pyrin, AIM (Absent in Melanoma), ASC (Apoptosis-associated speck-like protein containing a caspase recruitment domain) and DD (death domain)) domain containing polypeptide (I) comprising an amino acid sequence of at least 80% identity

to the amino acid sequence (S1) of PAN 2-6, pyrin 2 or ASC-2, where (I) is biologically active.

INDEPENDENT CLAIMS are included for the following:

(1) an isolated PAAD domain polypeptide (II) comprising a sequence which is 80% identical to amino acid sequence (S2) of PAN 2-6, pyrin 2 or ASC-2, is biologically active;

(2) an isolated NB-ARC domain polypeptide (III) comprising amino acid sequence (S3) of 80% identity to amino acids 147-465 or 196-512 or 93-273 or 183-372 of PAN 2-6 which is biologically active;

(3) an isolated leucine-rich repeat (LRR) domain polypeptide (IV) comprises amino acid sequence (S4) of 80% identity to amino acids 620-995 or 658 or 429-1031 of PAN-2,3 and 6 which is biologically active;

(4) an isolated peptide (V) comprising at least 10 contiguous amino acids of (S1);

(5) an isolated anti-PAAD antibody (VI) having specific reactivity with (I);

(6) a cell line producing the monoclonal antibody;

(7) an isolated nucleic acid molecule (VII) **encoding** (I) comprises a nucleic acid **encoding** (S1) or that hybridizes to nucleic acid molecule **encoding** (S1) under high stringent conditions, where (VII) **encodes** a biologically active (I);

(8) an isolated nucleic acid molecule (VIII) **encoding** (II) comprises a nucleic acid molecule **encoding** (S2) or a nucleic acid molecule that hybridizes to the nucleic acid molecule **encoding** (S2) under high stringent conditions, where (VIII) **encodes** a biologically active (II);

(9) an isolated nucleic acid molecule (IX) **encoding** (III) comprises a nucleic acid **encoding** (S3) or that binds to nucleic acid **encoding** (S3) under high stringent condition, where (IX) **encodes** a biologically active (III);

(10) an isolated nucleic acid molecule (X) **encoding** (IV) comprises a nucleic acid molecule **encoding** (S4) or that binds to nucleic acid **encoding** (S4) under high stringent condition, where (X) **encodes** a biologically active (IV);

(11) an oligonucleotide (XI) comprising at least 17 nucleotides capable of specifically hybridizing with cDNA of PAN 2-6, pyrin 2 or ASC-2 or its complement;

(12) an oligonucleotide (XII) comprising at least 50 nucleotides capable of specifically hybridizing with cDNA of PAN 2-6, pyrin 2 or ASC-2 or its complement;

(13) a vector containing (VII), (VIII), (IX) or (X);

(14) a recombinant cell containing (VII), (VIII), (IX) or (X); and

(15) decreasing the expression of (I) in a cell by introducing an antisense or dsRNA molecule into a cell which binds to cDNA of PAN 2-6, pyrin 2 or ASC-2.

ACTIVITY - Cytostatic; immunosuppressive; vulnerary; antiinflammatory; vasotropic; antiallergic; antiulcer; dermatological; cerebroprotective; cardiant; antiparkinsonian; nootropic; neuroprotective; anti-HIV. No supporting data is given.

MECHANISM OF ACTION - Gene therapy; inhibitor of NFkappaB activation.

10000 293N cells were seeded into 96 well plates and cells were transfected the following using Superfect transfection reagent with 10 ng of pNFkappaB-luc Renilla luciferase (pRL-TK) reporter vectors together with 100 ng of plasmids **encoding** proteins in the tumor necrosis factor- alpha (TNF) pathway (pCMV, TNFR1, pcDNA3 Traf2 or pcDNA3HA RIP) and either 400 ng of pcDNA3Myc (empty) or 400 ng of pcDNA3MycPAAD1-89 (PAAD). After 36 hours, cells were harvested and activity were determined using the dual luciferase system. The cells were stimulated with 10 ng TNF- alpha for 6-8 hours prior to lysis. For empty, the TNF- alpha

induction of NFkappaB activity was 21.05 and that of PAAD2 was 7.14. This results of NFkappaB activation indicated that expression of PAAD domain of PAN 2 significantly inhibited NFkappaB activation by TNF alpha . It was concluded that inhibition of NFkappaB activation by PAN 2 was mediated by the PAAD domain by expression of full length PAN 2 by transfection with pcDNA3MycPAN2 or pcNDA3MycPAAD 1-89 which was same.

USE - (XI) is useful for identifying (VII) in a sample. (VI) is useful for detecting the presence of (I) in a sample. (I)/(II) is useful for identifying (I)-associated polypeptide (PAP). (III) or (IV) is also useful for identifying PAP. (I), (II), (III), or (IV) is useful for identifying an effective agent that alters the association of (I), (II), (II) or (IV) with PAP such as ASC, ASC2, caspase-1, card10, Nod1, NIK, IKKi, JKB alpha and IKAP. (I) is useful for identifying an agent that modulates PAAD domain mediated inhibition of nuclear factor kappaB (NFkappaB) by contacting a cell that recombinantly express (I) or inducer of NFkappaB with a candidate agent and detecting the NFkappaB activity i.e. increase or decrease in NFkappaB activity in cell compared to a control cell indicates that the candidate agent modulates PADD domain mediated inhibition NFkappaB of activity. (III) is useful for identifying an agent that modulates the activity of NB-ARC domain of (I). (VIII) is useful for modulating the transcriptional activity of NFkappaB in a cell (all claimed). (I) or its functional fragments is useful in altering cellular or biochemical process such as apoptosis, NFkappaB induction, cytokine processing, cytokine receptor signaling caspase-mediated proteolysis or c-Jun N-terminal kinase activation, thus having modulating effect on cell life and death (apoptosis) inflammation, cell adhesion or other cellular or biochemical processes. (I) is useful for the production of (VI). (VII) is useful for producing (I), as hybridization probe for assaying PADD domain **encoding** gene or mRNA transcript or as primers or templates in PCR reaction for amplifying genes **encoding** (I). (I) is useful for treating cancer pathologies, keratinocyte, hyperplasia, neoplasia, keloid benign prostatic hypertrophy, inflammatory hyperplasia, fibrosis, smooth muscle cell proliferation in arteries following balloon angioplasty (restenosis), leukemia, lymphomas; inflammatory diseases such as allergies, arthritis, lupus, schrojen's syndrome, Crohn's disease and ulcerative colitis, graft versus host disease, stroke, heart failure, neurodegenerative diseases such as parkinson's and Alzheimer's disease, human immuno deficiency virus infection (HIV). (I) is useful for diagnosing cancer or monitoring cancer therapy.

Dwg.0/10

L26 ANSWER 28 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-719987 [68] WPIDS
CROSS REFERENCE: 1998-377655 [32]; 1998-377657 [32]; 2001-407216 [43]; 2002-642254 [69]; 2003-605660 [57]; 2003-615702 [58]; 2003-875016 [81]; 2005-099442 [11]
DOC. NO. CPI: C2003-197997
TITLE: New isolated receptor activator of **nuclear factor-kappa B** ligand polypeptide useful for **inducing** maturation of dendritic cells, enhancing allo-stimulatory capacity in dendritic cells, and promoting viability of T-cells.
DERWENT CLASS: B04 D16
INVENTOR(S): MARASKOVSKY, E
PATENT ASSIGNEE(S): (IMMV) IMMUNEX CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 2002169117 | A1 | 20021114 | (200368)* | | 49 |
| US 6649164 | B2 | 20031118 | (200376) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 2002169117 | A1 | Provisional | US 1996-59978P | 19961223 |
| | | Provisional | US 1997-77181P | 19970307 |
| | | Provisional | US 1997-64671P | 19971014 |
| | | Cont of | US 1997-995659 | 19971222 |
| | | Div ex | US 2000-577780 | 20000524 |
| | | | US 2001-877650 | 20010608 |
| US 6649164 | B2 | Provisional | US 1996-59978P | 19961223 |
| | | Provisional | US 1997-77181P | 19970307 |
| | | Provisional | US 1997-64671P | 19971014 |
| | | Cont of | US 1997-995659 | 19971222 |
| | | Div ex | US 2000-577780 | 20000524 |
| | | | US 2001-877650 | 20010608 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| US 2002169117 | A1 | Cont of | US 6242213 |
| US 6649164 | B2 | Cont of | US 6242213 |
| | | Div ex | US 6419929 |

PRIORITY APPLN. INFO: US 2001-877650 20010608; US
1996-59978P 19961223; US
1997-77181P 19970307; US
1997-64671P 19971014; US
1997-995659 19971222; US
2000-577780 20000524

AN 2003-719987 [68] WPIDS

CR 1998-377655 [32]; 1998-377657 [32]; 2001-407216 [43]; 2002-642254 [69]; 2003-605660 [57]; 2003-615702 [58]; 2003-875016 [81]; 2005-099442 [11]

AB US2002169117 A UPAB: 20050217

NOVELTY - An isolated receptor activator of nuclear factor-kappa B (NF-kappa B) ligand (RANKL) polypeptide (I) that:

(i) has a sequence of 294 and 317 amino acids, given in the specification;

(ii) is a RANKL polypeptide **encoded** by a DNA capable of hybridization to a DNA **encoding** polypeptides, which is biologically active; or

(iii) is a biologically active fragment of the polypeptides, is new.

DETAILED DESCRIPTION - An isolated receptor activator of NF-kappa B ligand (RANKL) polypeptide (I) is:

(i) a polypeptide having a fully defined sequence (S1) of 294 amino acids, given in the specification, where the polypeptide has an amino terminus chosen from an amino acid between positions 1 and 139, inclusive, and a carboxy terminus chosen from an amino acid between positions 290 and 294, inclusive;

(ii) a polypeptide having a fully defined sequence (S2) of 317 amino acids, given in the specification, where the polypeptide has an amino terminus chosen from an amino acid between positions 1 and 162, inclusive, and a carboxy terminus chosen from an amino acid between 313 and 317,

inclusive;

(iii) a RANKL polypeptide **encoded** by a DNA capable of hybridization to a DNA **encoding** (i) or (ii) under stringent conditions, which is biologically active; and

(iv) fragments of (i), (ii) or (iii) which are biologically active.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated DNA (II) that is:

(i) a DNA **encoding** a protein having a fully defined sequence (S3) of 1630 nucleotides, given in the specification, where the protein has an amino terminus chosen from an amino acid between positions 1 or 48 and 139, inclusive, and a carboxy terminus chosen from an amino acid between positions 290 and 294, inclusive;

(ii) a DNA **encoding** a protein having a fully defined sequence (S4) of 954 nucleotides, given in the specification, where the protein has an amino terminus chosen from an amino acid between positions 1 or 69 and 162, inclusive, and a carboxy terminus chosen from an amino acid between positions 313 and 317 inclusive;

(iii) DNA molecules capable of hybridization to the DNA of (i) or (ii) under stringent conditions, which **encode** biologically active RANKL; or

(iv) DNA molecules **encoding** fragments of proteins **encoded** by the (i) - (iii), respectively;

(2) a recombinant vector (III) comprising (II);

(3) a host cell (IV) transformed with (III);

(4) preparing (I);

(5) an isolated DNA chosen from oligonucleotides of about 17, 25 and 30 nucleotides in length, which is a fragment of (S3) or (S4); and

(6) an antibody (IV) immunoreactive with (I).

ACTIVITY - Immunomodulatory; Antiinflammatory.

MECHANISM OF ACTION - Inflammatory or immune response regulator. The influence of RANKc and hRANKL on activated T cell growth was as follows. The addition of transdermal growth factor (TGF) beta to anti-CD3 activated human peripheral blood T lymphocytes induced proliferation arrest and ultimately death of most lymphocytes within the first few days of culture. The effect of RANK:RANKL interactions on TGF beta -treated T cells by adding RANKc or soluble human RANKL to T cell cultures was as follows. Human peripheral blood T (PBT) cells (7 multiply 105) were cultured for six days on anti-CD3 (OKT3, 5 micro g/ml) and anti-FLAG (Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys; M1, 5 micro g/ml) coated 24 well plates in the presence of TGF beta (1 ng/ml) and interleukin (IL)-4 (10 ng/ml), with or without recombinant FLAG-tagged soluble hRANKL (1 micro g/ml) or RANKc (10 micro g/ml). Viable T cell recovery was determined by triplicate trypan blue countings. The addition of RANKc significantly reduced the number of viable T cells recovered after six days, where soluble RANKL greatly increased the recovery of viable T cells. Thus endogenous or exogenous RANKL enhances the number of viable T cells generated in the presence of TGF beta .

USE - (I) Is useful for inducing maturation of dendritic cells (DC), comprising contacting CD1a+DC with an amount of (I) sufficient to result in decreased levels of CD1b/c expression on the DC, under conditions promoting viability of the DC, and allowing the DC to mature. (I) Is useful for enhancing allo-stimulatory capacity in DC, comprising contacting CD1a+DC with an amount of (I) sufficient to increase the allo-stimulatory capacity of the DC in a mixed lymphocyte reaction (MLR), under conditions promoting viability of the DC, and allowing DC to present antigens to T cells. (I) Is useful for promoting viability of T-cells in the presence of transdermal growth factor (TGF) beta , which involves contacting T cells that have been expressed to TGF beta with an amount of (I) sufficient to increase the number of T cells that remain viable in the

presence of TGF beta , under conditions that would promote viability of T cells in the absence of TGF beta , and allowing the T cells to influence T cell tolerance (all claimed). (I) Is useful in augmenting an immune response for screening potential inhibitors. (I) Is useful for treatment in regulating immune or inflammatory responses.
Dwg.0/5

L26 ANSWER 29 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-605660 [57] WPIDS
CROSS REFERENCE: 1998-377655 [32]; 1998-377657 [32]; 2001-407216 [43]; 2002-642254 [69]; 2003-615702 [58]; 2003-719987 [68]; 2003-875016 [81]; 2005-099442 [11]
DOC. NO. CPI: C2003-164787
TITLE: Novel RANKL, ligand of receptor activator of **nuclear factor-kappa B** useful for **inducing** maturation in dendritic cells and enhancing allo-stimulatory capacity of dendritic cells.
DERWENT CLASS: B04 D16
INVENTOR(S): ANDERSON, D M; GALIBERT, L; MARASKOVSKY, E
PATENT ASSIGNEE(S): (IMMV) IMMUNEX CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 2002086826 | A1 | 20020704 | (200357)* | | 49 |
| US 6740522 | B2 | 20040525 | (200435) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 2002086826 | A1 | Provisional | US 1996-59978P | 19961223 |
| | | Provisional | US 1997-77181P | 19970307 |
| | | Provisional | US 1997-64671P | 19971014 |
| | | Div ex | US 1997-995659 | 19971222 |
| | | Div ex | US 2000-577780 | 20000524 |
| | | | US 2001-865363 | 20010525 |
| US 6740522 | B2 | Provisional | US 1996-59978P | 19961223 |
| | | Provisional | US 1997-77181P | 19970307 |
| | | Provisional | US 1997-64671P | 19971014 |
| | | Div ex | US 1997-995659 | 19971222 |
| | | Div ex | US 2000-577780 | 20000524 |
| | | | US 2001-865363 | 20010525 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| US 6740522 | B2 | Div ex | US 6242213 |
| | | Div ex | US 6419929 |

PRIORITY APPLN. INFO: US 2001-865363 20010525; US 1996-59978P 19961223; US 1997-77181P 19970307; US 1997-64671P 19971014; US 1997-995659 19971222; US 2000-577780 20000524

AN 2003-605660 [57] WPIDS
CR 1998-377655 [32]; 1998-377657 [32]; 2001-407216 [43]; 2002-642254 [69]; 2003-615702 [58]; 2003-719987 [68]; 2003-875016 [81]; 2005-099442 [11]
AB US2002086826 A UPAB: 20050217
NOVELTY - An isolated RANKL (ligand of receptor activator of nuclear factor-kappa B (NF-kB)) polypeptide (I) with a sequence (S1, murine) of 294 amino acids (aa) and an amino terminus between aa 1-139 and carboxy terminus between aa 290-294 of (S1), or a sequence (S2, human) of 317 aa given in the specification and amino terminus between aa 1-162 and carboxy terminus between aa 313-317 of (S2), is new.

DETAILED DESCRIPTION - (I) comprises a polypeptide with (S1) and an amino terminus between aa 1-139, and a carboxy terminus between aa 290-294 of (S1), or (S2) and amino terminus between aa 1-162, and a carboxy terminus between aa 313-317 of (S2), **encoded** by a deoxyribonucleic acid (DNA) that hybridizes to a DNA **encoding** (S1) or (S2) under stringent conditions, which is biologically active, or biologically active fragments of the sequences.

INDEPENDENT CLAIMS are also included for:

(1) an isolated DNA (II) **encoding** (I), or a soluble RANKL protein having (S1) and an amino terminus between aa 48-139, and a carboxy terminus between aa 290-294 of (S1), or (S2) and amino terminus between aa 69-162, and a carboxy terminus between aa 313-317 of (S2), or comprising a DNA that hybridizes to a DNA **encoding** (S1) or (S2) under stringent conditions, which is biologically active, or biologically active fragments of the above;

(2) a recombinant expression vector (III) comprising (II);

(3) a host cell (IV) transformed or transfected with (III);

(4) preparing (I);

(5) an isolated DNA chosen from oligonucleotides of at least 17, 25 or 30 nucleotides in length, which is fragment of the DNA of a sequence of 1630 or 954 bp defined in the specification; and

(6) an antibody (VI) immunoreactive with (I).

ACTIVITY - None given.

MECHANISM OF ACTION - Regulator of immune and inflammatory responses. No suitable data given.

USE - (I) is useful for inducing maturation of dendritic cells (DC), by contacting CD1a+ DC with (I) to decrease levels of CD1b/c expression on DC, under conditions promoting viability of DC, and allowing DC to mature. (I) is also useful for enhancing allo-stimulatory capacity in DC, by contacting CD1a+DC with (I) to increase the allo-stimulatory capacity of DC in a mixed lymphocyte reaction (MLR), under conditions promoting viability of DC, and allowing DC to present antigens to T cells and for promoting viability of T cells in the presence of transforming growth factor beta (TGF beta ), by contacting T cells that is exposed to TGF beta with (I) to increase the number of T cells that remain viable in the presence of TGF beta , under conditions that would promote viability of T cells in the absence of TGF beta , and allowing the T cells to influence T cell tolerance (claimed). (I) is useful for preparing kits that are used to detect soluble RANK or RANKL or monitoring RANK-related activity, for screening inhibitors of RANK, for structure-based design of RANKL inhibitors, and in augmenting an immune response. (I) is also useful as a vaccine adjuvant or as therapeutic agent to upregulate an immune response for e.g. in infectious disease. (II) is useful for expressing recombinant proteins, as probes for analysis (quantitative or qualitative) of the presence or distribution of RANKL transcripts and detecting the presence of RANKL nucleic acids. (I) and (II) are useful for preparing pharmaceutical compositions, and for developing antibodies to RANKL.
Dwg.0/5

L26 ANSWER 30 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:218507 HCAPLUS
DOCUMENT NUMBER: 136:367476
TITLE: A novel NF-κB-inducing kinase-MAPK signaling pathway up-regulates NF-κB activity in melanoma cells
AUTHOR(S): Dhawan, Punita; Richmond, Ann
CORPORATE SOURCE: Department of Veterans Affairs, Nashville, TN, 37212, USA
SOURCE: Journal of Biological Chemistry (2002), 277(10), 7920-7928
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Constitutive activation of NF-κB is an emerging hallmark of various types of tumors including breast, colon, pancreatic, ovarian, and melanoma. In melanoma cells, the basal expression of the CXC chemokine, CXCL1, is constitutively up-regulated. This up-regulation can be attributed in part to constitutive activation of NF-κB. Previous studies have shown an elevated basal IκB kinase (IKK) activity in Hs294T melanoma cells, which leads to an increased rate of IκB phosphorylation and degradation This increase in IκB-α phosphorylation and degradation leads to an .apprx.19-fold higher nuclear localization of NF-κB. However, the upstream IKK kinase activity is up-regulated by only about 2-fold and cannot account for the observed increase in NF-κB activity. We now demonstrate that NF-κB-inducing kinase (NIK) is highly expressed in melanoma cells, and IKK-associated NIK activity is enhanced in these cells compared with the normal cells. Kinase-dead NIK blocked constitutive NF-κB or CXCL1 promoter activity in Hs294T melanoma cells, but not in control normal human epidermal melanocytes. Transient overexpression of wild type NIK results in increased phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2), which is inhibited in a concentration-dependent manner by PD98059, an inhibitor of p42/44 MAPK. Moreover, the NF-κB promoter activity decreased with overexpression of dominant neg. ERK expression constructs, and EMSA analyses further support the hypothesis that ERK acts upstream of NF-κB and regulates the NF-κB DNA binding activity. Taken together, our data implicate involvement of IκB kinase and MAPK signaling cascades in NIK-induced constitutive activation of NF-κB.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 31 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:13834 BIOSIS
DOCUMENT NUMBER: PREV200300013834
TITLE: CD40 regulates the processing of NF-kappaB2 p100 to p52.
AUTHOR(S): Coope, H. J.; Atkinson, P. G. P.; Huhse, B.; Belich, M.; Janzen, J.; Holman, M. J.; Klaus, G. G. B.; Johnston, L. H.; Ley, S. C. [Reprint Author]
CORPORATE SOURCE: Division of Immune Cell Biology, National Institute for Medical Research, London, NW7 1AA, UK
sley@nimr.mrc.ac.uk
SOURCE: EMBO (European Molecular Biology Organization) Journal, (October 15 2002) Vol. 21, No. 20, pp. 5375-5385. print.

ISSN: 0261-4189 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Dec 2002
Last Updated on STN: 25 Dec 2002

AB The nf-kb2 gene **encodes** the cytoplasmic NF-kappaB inhibitory protein p100 from which the active p52 NF-kappaB subunit is derived by proteasome-mediated proteolysis. Ligands which stimulate p100 processing to p52 have not been defined. Here, ligation of CD40 on transfected 293 cells is shown to trigger p52 production by stimulating p100 ubiquitylation and subsequent proteasome-mediated proteolysis. CD40-mediated p52 accumulation is dependent on de novo protein synthesis and triggers p52 translocation into the nucleus to generate active NF-kappaB dimers. Endogenous CD40 ligation on primary murine splenic B cells also stimulates p100 processing, which results in the delayed nuclear translocation of p52-RelB dimers. In both 293 cells and primary splenic B cells, the ability of CD40 to trigger p100 processing requires functional NF-kappaB-inducing kinase (NIK). In contrast, NIK activity is not required for CD40 to stimulate the degradation of IkappaBalpha in either cell type. The regulation of p100 processing by CD40 is likely to be important for the transcriptional regulation of CD40 target genes in adaptive immune responses.

L26 ANSWER 32 OF 54 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002236887 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11934728
TITLE: Nuclear factor-kappaB activation in alveolar macrophages requires IkappaB kinase-beta, but not **nuclear factor-kappaB inducing** kinase.
AUTHOR: Conron Matthew; Andreakos Evangelos; Pantelidis Panagiotis; Smith Clive; Beynon Huw L C; Dubois Roland M; Foxwell Brian M J
CORPORATE SOURCE: Kennedy Institute of Rheumatology, Hammersmith, London, United Kingdom.. conronm@svhm.org.au
SOURCE: American journal of respiratory and critical care medicine, (2002 Apr 1) 165 (7) 996-1004.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020429
Last Updated on STN: 20020510
Entered Medline: 20020509

AB Cytokine mediated activation of alveolar macrophages (AMs) is an important event in the pathogenesis of fibrosing alveolitis (FA). Through membrane-associated antigens, cytokines (e.g., tumor necrosis-factor-alpha and interleukin-1) are believed to activate a common kinase cascade that initiates the cytoplasmic degradation of IkappaB and nuclear translocation of "nuclear factor-kappaB" (NF-kappaB). In the nucleus, NF-kappaB promotes the transcription of genes **encoding** chemokines and cytokines involved in chronic inflammation. Preventing cytokine-mediated NF-kappaB activation is a potential strategy for attenuating the lung injury that occurs in FA. Previously, we have demonstrated that, unlike AMs from healthy volunteers, AMs from patients with inflammatory lung diseases express the coxsackie/adenovirus receptor and the alphav integrins required for adenovirus (Adv) infection. This property allows Adv-mediated transgene delivery to diseased, but not normal, AMs and

analysis of molecular pathways involved in gene transcription. In this study, AMs were infected with Adv constructs expressing a defective beta subunit of IkappaB kinase (AdvIKKbetakd) and a defective NF-kappaB inducing kinase (AdvNIKkd) to investigate the contribution of these molecules to NF-kappaB activation. We observed that IKKbeta, but not NIK, was required for NF-kappaB activation. The results of this study identify IKKbeta, but not NIK, as a potential therapeutic target in diseases that involve NF-kappaB-dependent gene transcription.

L26 ANSWER 33 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:283597 HCAPLUS
DOCUMENT NUMBER: 137:45926
TITLE: Proteolysis-inducing factor differentially influences transcriptional regulation in endothelial subtypes
AUTHOR(S): Watchorn, T. M.; Waddell, I.; Ross, J. A.
CORPORATE SOURCE: Molecular Immunology Group, Department of Clinical and Surgical Sciences, University of Edinburgh, Edinburgh, EH3 9YW, UK
SOURCE: American Journal of Physiology (2002), 282(4, Pt. 1), E763-E769
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Proteolysis-inducing factor (PIF) is a novel sulfated glycoprotein initially identified as a protein capable of triggering muscle proteolysis during the process of cancer cachexia. Only skeletal muscle and liver exhibit substantial binding of PIF in adult tissue. Here, the authors demonstrate that PIF induces transcriptional regulation in both the liver endothelial cell line SK-HEP-1 and in human umbilical vein endothelial cells (HUVECs) but not in pulmonary artery endothelial cells. PIF differentially induces activation of nuclear factor-κB, resulting in the induction of proinflammatory cytokines [interleukin (IL)-8 and IL-6] and increased expression of the cell surface proteins intercellular adhesion mol.-1 and vascular cell adhesion mol. in SK-HEP-1 and HUVECs only. In addition, PIF induces the shedding of syndecans from the cell surface. Syndecans are involved in wound repair, metastasis of cancers, and embryonic development. These results suggest that PIF may play addnl. roles in the proinflammatory response observed in cancer cachexia but may also have a role without the cachectic process.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 34 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:115791 HCAPLUS
DOCUMENT NUMBER: 138:319591
TITLE: Inducing endotoxin tolerance reduces surgical stress
AUTHOR(S): Kojima, Junichi; Mimura, Yoshikazu; Hiki, Naoki; Ogawa, Toshihisa; Hatao, Fumihiko; Kaminishi, Norio
CORPORATE SOURCE: Graduate School of Medicine, University of Tokyo, Japan
SOURCE: Endotokishin Kenkyu (2002), 5, 173-180
CODEN: EKNEBO
PUBLISHER: Igaku Tosho Shuppan K.K.
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The authors examined induction of endotoxin tolerance to reduce surgical stress. Pre-administration of LPS induced endotoxin tolerance to reduced inflammatory cytokine induction and AST level. Many MAP kinases are

involved in the induction of tolerance. The induction of tolerance can be used to reduce infection after surgery.

L26 ANSWER 35 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2001:747850 HCAPLUS
DOCUMENT NUMBER: 135:300247
TITLE: Human NF-κ B inducing factor and cDNA and methods for drug screening and inhibition of inflammation
INVENTOR(S): Kaplow, June; Haws, Thomas; Rosier, Marie; Denefle, Patrice
PATENT ASSIGNEE(S): Aventis Pharmaceuticals Products Inc., USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2001074900 | A2 | 20011011 | WO 2001-US10719 | | 20010402 |
| WO 2001074900 | A3 | 20020502 | | | |
| WO 2001074900 | C2 | 20030306 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | | |
| US 2003170862 | A1 | 20030911 | US 2001-823119 | | 20010330 |
| CA 2404688 | AA | 20011011 | CA 2001-2404688 | | 20010402 |
| BR 2001009721 | A | 20030204 | BR 2001-9721 | | 20010402 |
| EP 1290023 | A2 | 20030312 | EP 2001-920925 | | 20010402 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | | |
| JP 2003529360 | T2 | 20031007 | JP 2001-572589 | | 20010402 |
| NZ 521786 | A | 20040730 | NZ 2001-521786 | | 20010402 |
| ZA 2002007767 | A | 20040326 | ZA 2002-7767 | | 20020926 |
| NO 2002004656 | A | 20021128 | NO 2002-4656 | | 20020927 |
| PRIORITY APPLN. INFO.: | | | US 2000-193905P | P | 20000331 |
| | | | GB 2000-18307 | A | 20000726 |
| | | | WO 2001-US10719 | W | 20010402 |

AB The present invention is directed to **nuclear factor** . **kappa.B** (NF.**kappa.B**)-**inducing factor** polypeptides (**NFIF** polypeptides) which are capable of inducing NFκ B. The present invention includes within its scope two **NFIF** proteins, a 453-amino acid and a 364-amino acid isoforms generated by alternative pre-mRNA splicing. Also included are methods and compns. for increasing NFκ B induction in a patient, methods and compns. for lowering NFκ B induction in a patient, methods for inhibiting inflammation, and methods for manufacture of a medicament intended for the treatment and/or prevention of an NFκ B-regulated inflammatory response. In addition, methods for determining whether a test compound

inhibits or enhances the activity of **NFIF** polypeptides are provided.

L26 ANSWER 36 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-158378 [16] WPIDS
CROSS REFERENCE: 1999-253865 [21]
DOC. NO. CPI: C2001-046924
TITLE: Novel human kinase IKAP polypeptide useful in diagnosis, therapy, biopharmaceutical industry and for screening for modulators of the polypeptide.
DERWENT CLASS: B04
INVENTOR(S): BAEUERLE, P; COHEN, L
PATENT ASSIGNEE(S): (TULA-N) TULARIK INC
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 6172195 | B1 | 20010109 | (200116)* | | 15 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| US 6172195 | B1 Div ex | US 1997-971244 | 19971116 |
| | | US 1999-286891 | 19990406 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| US 6172195 | B1 Div ex | US 5891719 |

PRIORITY APPLN. INFO: US 1997-971244 19971116; US 1999-286891 19990406
AN 2001-158378 [16] WPIDS
CR 1999-253865 [21]
AB US 6172195 B UPAB: 20010323
NOVELTY - An isolated polypeptide (I) comprising a sequence of 1332 amino acids fully defined in the specification or its fragments selected from residues 1-10, 29-41, 75-87, 92-109, 132-141, 192-205, 258-269, 295-311, 316-330, 373-382, 403-422, 474-485, 561-576, 683-697, 768-777, 798-813, 1054-1067, 1181-1192, 1273-1282, 1283-1294, 1295-1312 and 1313-1332, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for screening (M) for an agent which modulates the interaction of (I) to a binding target involving incubating a mixture comprising (I), a binding target of (I) and a candidate agent, under conditions where, but for the presence of the agent, (I) specifically binds the binding target at a reference affinity and detecting the binding affinity of (I) to the binding target to determine an agent-biased affinity, where a difference between the agent-biased affinity and the reference affinity indicates that the agent modulates the binding of (I) to the binding target.

USE - Compositions containing (I) are useful in diagnosis, therapy and in biopharmaceutical industry (e.g., as immunogens, reagents for isolating other transcriptional regulators, reagents for screening chemical libraries for lead pharmacological agents, etc). (I) is useful for screening for agents which modulate the activity of (I) and the agents identified are useful in pharmaceutical industries for animal and human

trials, for e.g., the reagents may be derivatized and rescreened in vitro and in vivo assays to optimize the activity and minimize toxicity for pharmaceutical development. Genes **encoding** (I) are useful as translatable transcripts, hybridization probes, PCR primers, diagnostic nucleic acids, etc., and in therapy to modulate cellular expression or intracellular concentration or availability of active IKAP. Dwg.0/1

L26 ANSWER 37 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:712272 HCAPLUS
DOCUMENT NUMBER: 136:19094
TITLE: Calmodulin-dependent kinase II mediates T cell receptor/CD3- and phorbol ester-induced activation of IκB kinase
AUTHOR(S): Hughes, Kate; Edin, Sofia; Antonsson, Asa; Grundstrom, Thomas
CORPORATE SOURCE: Department of Molecular Biology, Umea University, Umea, 901 87, Swed.
SOURCE: Journal of Biological Chemistry (2001), 276(38), 36008-36013
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Numerous fundamental biol. processes involve the NFκB family of transcription factors. The mechanisms by which this family of proteins is regulated are therefore of widespread importance. In most cells, NFκB is bound to inhibitory IκB proteins and sequestered in the cytoplasm. NFκB-inducing signals result in activation of a large multisubunit kinase complex, IKK, which phosphorylates IκB. IκB is subsequently degraded, releasing NFκB, which translocates to the nucleus. The authors previously reported that inhibitors of the calcium-binding protein calmodulin (CaM) prevent phorbol ester-induced phosphorylation of IκB. Here the authors show that KN93, an inhibitor of CaM-dependent kinases (CaMKs), also inhibits the phosphorylation of IκB. The effect of both CaM and CaMK inhibitors on IκB phosphorylation is due to the inhibition of the activity of CaMK II because neither drug has any effect when a derivative of CaMK II that is insensitive to these inhibitors is expressed. When CaMK II is inhibited, phorbol ester is no longer able to activate IKK, placing CaMK II in the signaling pathway that leads to IKK activation. CaM and CaMK inhibitors also block T cell receptor/CD3-induced activation but have no effect on the ability of the cytokine tumor necrosis factor α or the phosphatase inhibitor calyculin A to induce degradation of IκB. Finally the authors show that expression of a constitutively active CaMK II results in the activation of NFκB. The results identify CaMK II as a mediator of IKK activation specifically in response to T cell receptor/CD3 and phorbol ester stimulation.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 38 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:832590 HCAPLUS
DOCUMENT NUMBER: 136:101071
TITLE: NF-κB-inducing kinase is dispensable for activation of NF-κB in inflammatory settings but essential for lymphotoxin β receptor activation of NF-κB in primary human fibroblasts

AUTHOR(S): Smith, Clive; Andreakos, Evangelos; Crawley, James B.; Brennan, Fionula M.; Feldmann, Marc; Foxwell, Brian M. J.
CORPORATE SOURCE: Kennedy Institute of Rheumatology Division, Imperial College School of Medicine, London, W6 8LH, UK
SOURCE: Journal of Immunology (2001), 167(10), 5895-5903
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The transcription factor NF-κB is of major importance in the biol. of pro-inflammatory cytokines, such as TNF-α and IL-1α, and thereby is intimately involved in the process of inflammation. Understanding the mechanisms by which NF-κB is activated in response to inflammatory stimuli has become a major goal of inflammation research. The discovery of NF-κB-inducing kinase (NIK) as a TNFR-associated factor-interacting enzyme and a potential activator of the IκBα-kinase complex appeared to have identified an important element of the NF-κB activation pathway, a view that was supported by several subsequent studies. However, recent expts. in the alymphoplasia (aly/aly) mouse, which has missense point mutation (G885R) in NIK, has challenged that view. The reasons for the discrepancy between the different studies is unclear and could be due to multiple factors, such as cell type, species of cell, or primary vs transformed cell lines. One system that has not been investigated is primary human cells. Using an adenoviral vector **encoding** kinase-deficient NIK, the authors have investigated the role of NIK in LPS, IL-1, TNF-α, and lymphotoxin (LT) βR signaling in primary human cells and TNF-α expression from rheumatoid tissue. These data show that, in the primary systems tested, NIK has a restricted role in LTβR signaling and is not required by the other stimuli tested. Also, there is no apparent role for NIK in the process of TNF-α production in human rheumatoid arthritis. These data also highlight the potential problems in extrapolating the function of signaling pathways between primary and transfected cell lines.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 39 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:439955 BIOSIS
DOCUMENT NUMBER: PREV200100439955
TITLE: HIV-1 Tat can substantially enhance the capacity of NIK to induce IkappaB degradation.
AUTHOR(S): Li, Xuguang; Josef, Juliana; Marasco, Wayne A. [Reprint author]
CORPORATE SOURCE: Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, 44 Binney Street, JFB 824, Boston, MA, 02115, USA
wayne_marasco@dfci.harvard.edu
SOURCE: Biochemical and Biophysical Research Communications, (August 24, 2001) Vol. 286, No. 3, pp. 587-594. print.
CODEN: BBRCA9. ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002

AB The human immunodeficiency virus type 1 (HIV-1) Tat is a virally **encoded** protein that dramatically upregulates viral replication

through interactions with the HIV-1 5' long terminal repeat (LTR) and cellular transcription factors. The HIV-1 LTR is divided into three major regions: modulatory, core and TAR. The modulatory region contains numerous cis-acting sequences for the binding of transcription factors including NF-kappaB, NF-AT, and AP-1. In several reports, Tat has been found to induce NF-kappaB activation of the HIV-1 LTR, while in other studies Tat has been reported to have no effect on activation of NF-kappaB. These discrepancies may arise from differences in experimental conditions such as the source of Tat (exogenous versus endogenous), the detection methods for NF-kappaB activation (DNA binding capability versus IkappaB degradation), and the types of reporters used (HIV-1 versus non-HIV-1 derived). To reconcile these differences we examined the effect of endogenous Tat on NF-kappaB activation, on IkappaB degradation and its interaction with upstream MAP3Ks. We demonstrate that although an 80% reduction in Tat-induced HIV-1 LTR activity can be detected if the kappaB binding sites are mutated, surprisingly endogenous Tat (expressed intracellularly by transfection) lacks direct effect on IkappaB degradation. Further analysis demonstrates that although Tat alone lacks direct effect on IkappaBalpha degradation or dissociation from NF-kappaB, Tat can substantially enhance the capacity of NF-kappaB-inducing kinase (NIK), but not MEKK1, to accelerate degradation of IkappaB. We propose a model to explain these collective experimental findings.

L26 ANSWER 40 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:211503 HCAPLUS
DOCUMENT NUMBER: 135:299392
TITLE: Proteolysis-inducing factor regulates hepatic gene expression via the transcription factors NF-κB and STAT3
AUTHOR(S): Watchorn, T. M.; Waddell, I.; Dowidar, N.; Ross, J. A.
CORPORATE SOURCE: Molecular Immunology Group, Department of Clinical and Surgical Sciences, Edinburgh University, UK
SOURCE: FASEB Journal (2001), 15(3), 562-564
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Proteolysis-inducing factor (PIF) of mol. weight 24,000 appears to fulfill the function of triggering muscle proteolysis during the process of cancer cachexia. However, comprehensive tissue screening demonstrated that only skeletal muscle and liver exhibit substantial binding of PIF. The biol. effect of PIF on hepatic gene expression in primary cultures of human hepatocytes and on the human cell line HepG2 via the NF-κB and STAT3 pathways was investigated. NF-κB activation was demonstrated using both IL-8 and IL-6 production ICAM-1 expression in hepatocytes and nuclear exts. prepared for NFκB were used to study the effect of PIF on STAT3 activation. Results showed that PIF can induce NF-κB and STAT3 in isolated human hepatocytes with the resultant expression of proinflammatory cytokines, adhesion mols., and acute phase proteins. PIF may thus play role in cancer cachexia, in addition to its effects on skeletal muscle, by contributing to a continuous cycle of cytokine and acute-phase protein production

L26 ANSWER 41 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:266161 HCAPLUS
DOCUMENT NUMBER: 135:15917
TITLE: NF-κB-inducing kinase regulates the processing of NF-κB2 p100

AUTHOR(S): Xiao, Gutian; Harhaj, Edward W.; Sun, Shao-Cong
CORPORATE SOURCE: Department of Microbiology and Immunology, Pennsylvania State University College of Medicine, Hershey, PA, 17033, USA
SOURCE: Molecular Cell (2001), 7(2), 401-409
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Processing of the nfκb2 gene product p100 to generate p52 is an important step in NF-κB regulation. We show that this step is neg. regulated by a processing-inhibitory domain (PID) within p100 and pos. regulated by the NF-κB-inducing kinase (NIK). While the PID suppresses the constitutive processing of p100, NIK induces p100 processing by stimulating site-specific phosphorylation and ubiquitination of this precursor protein. Further, a natural mutation of the gene **encoding** NIK in alymphoplasia (aly) mice cripples the function of NIK in p100 processing, causing a severe defect in p52 production These data suggest that NIK is a specific kinase regulating p100 processing and explain why the aly and nfκb2 knockout mice exhibit similar immune deficiencies.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 42 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:222138 BIOSIS
DOCUMENT NUMBER: PREV200200222138
TITLE: Flice-inhibitory protein (FLIP) inhibits NF-KB signaling and is associated with an increased susceptibility to Fas-mediated apoptosis in differentiated HT-29 cells.
AUTHOR(S): Russo, Maria Pia [Reprint author]; Sartor, Ryan Balfour [Reprint author]; Jobin, Christian [Reprint author]
CORPORATE SOURCE: Univ of North Carolina, Chapel Hill, NC, USA
SOURCE: Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.696-A.697. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002

L26 ANSWER 43 OF 54 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000253235 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10790423
TITLE: Alymphoplasia (aly)-type nuclear factor kappaB-inducing kinase (NIK) causes defects in secondary lymphoid tissue chemokine receptor signaling and homing of peritoneal cells to the gut-associated lymphatic tissue system.
AUTHOR: Fagarasan S; Shinkura R; Kamata T; Nogaki F; Ikuta K; Tashiro K; Honjo T

CORPORATE SOURCE: Department of Medical Chemistry, Faculty of Medicine, Kyoto University, Kyoto, Japan.
SOURCE: Journal of experimental medicine, (2000 May 1) 191 (9) 1477-86.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000613
Last Updated on STN: 20030221
Entered Medline: 20000530

AB Alymphoplasia (aly) mice, which carry a point mutation in the **nuclear factor kappaB-inducing** kinase (NIK) **gene**, are characterized by the systemic absence of lymph nodes and Peyer's patches, disorganized splenic and thymic architectures, and immunodeficiency. Another unique feature of aly/aly mice is that their peritoneal cavity contains more B1 cells than normal and aly/+ mice. Transfer experiments of peritoneal lymphocytes from aly/aly mice into recombination activating gene (RAG)-2(-/-) mice revealed that B and T cells fail to migrate to other lymphoid tissues, particularly to the gut-associated lymphatic tissue system. In vivo homing defects of aly/aly peritoneal cells correlated with reduction of their in vitro chemotactic responses to secondary lymphoid tissue chemokine (SLC) and B lymphocyte chemoattractant (BLC). The migration defect of aly/aly lymphocytes was not due to a lack of expression of chemokines and their receptors, but rather to impaired signal transduction downstream of the receptors for SLC, indicating that NIK is involved in the chemokine signaling pathway known to couple only with G proteins. The results showed that the reduced serum levels of immunoglobulins (Igs) and the absence of class switch to IgA in aly/aly mice are due, at least in part, to a migration defect of lymphocytes to the proper microenvironment where B cells proliferate and differentiate into Ig-producing cells.

L26 ANSWER 44 OF 54 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2001013607 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11007944
TITLE: Oxidative stress interference with the nuclear factor-kappa B activation pathways.
AUTHOR: Schoonbroodt S; Piette J
CORPORATE SOURCE: Laboratory of Virology & Immunology, Institute of Pathology B23, University of Liege, B-4000 Liege, Belgium.
SOURCE: Biochemical pharmacology, (2000 Oct 15) 60 (8) 1075-83.
Ref: 84
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20020420
Entered Medline: 20001031

AB While intracellular redox balance is tightly controlled in many cell types, its modification leads to important cellular changes derived, in part, from a modification of the pattern of gene expression. This

modification relies on many transcription factors whose activities are either increased or reduced by a disbalance of the redox environment. Among these transcription **factors, nuclear factor-kappa** B (NF-**kappa B**) plays a pivotal role in **inducing genes** involved in the control of the immune system as well as in the response to injury and infection. Because NF-kappa B can be induced in many cells by a diverse set of stimulating agents, it has been proposed that agents activating it do so by increasing oxidative stress within the cell. However, this model was not found to be universal, since the dependence between NF-kappa B activation and intracellular reactive oxygen species (ROS) generation was only detected in certain cell lines. The origin of this dependency is still unknown, but could very well be situated in a particular kinase or in adaptator molecules of the signaling cascade, leading to inhibitor kappa B alpha (I kappa B alpha phosphorylation. On the other hand, NF-kappa B can be activated by oxidants in many cell types, but this activation is well characterized only in lymphocytes. This activation is distinct from that of classical activators such as proinflammatory cytokines and phorbol esters, because the activation mechanisms appear to converge on a particular tyrosine residue of I kappa B-alpha instead of the two classical N-terminal serines. The nature of the protein kinases or protein phosphatases involved in this process is still undetermined. It will be a challenge in the future to identify the kinases/phosphatases activated by oxidants and to discover why ROS are required in some cells to turn on the transduction pathway leading to NF-kappa B activation by physiological stimuli.

L26 ANSWER 45 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2000:734582 HCAPLUS
DOCUMENT NUMBER: 134:3982
TITLE: Tumor-necrosis-factor-receptor-associated factor 6, NF-κB-inducing kinase and IκB kinases mediate IgE isotype switching in response to CD40
AUTHOR(S): Brady, Kevin; Fitzgerald, Stephen; Moynagh, Paul N.
CORPORATE SOURCE: Department of Pharmacology, University College Dublin, Blackrock, Ire.
SOURCE: Biochemical Journal (2000), 350(3), 735-740
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The process of IgE switching requires the prior transcription of the unrearranged Cε gene, which leads to its recombination with the VDJ region. The activation of NF-κB by CD40 is a key process in facilitating this transcription by promoting the activation of the Cε promoter. The present study explores the uncharacterized signaling pathways employed by CD40 in activating NF-κB by the overexpression of genes **encoding** wild-type and dominant-neg. forms of the signaling components tumor necrosis factor receptor-associated factor 6 (TRAF-6), NF-κB-inducing kinase (NIK), IκB kinase (IKK)-1, and IKK-2 in the BJAB B-cell line. The overexpression of TRAF-6 or NIK was sufficient to activate NF-κB and the Cε promoter, whereas their dominant-neg. counterparts decreased the ability of CD40 to activate NF-κB and the Cε promoter. The over-expression of wild-type IKK-1 or IKK-2 seemed to cause toxic effects on the cells, whereas the dominant-neg. forms were selective in their blockade of NF-κB and the Cε promoter. Thus, CD40 employs TRAF-6, which presumably recruits NIK, which in turn employs IKK-1/IKK-2 to activate NF-κB and the Cε promoter, the prologue to IgE switching.

These findings define a crucially important pathway in the generation of allergic states.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 46 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-384722 [32] WPIDS
CROSS REFERENCE: 1999-080407 [07]; 1999-468406 [39]
DOC. NO. CPI: C1999-113066
TITLE: Screening for agents which modulate the interaction of IKK-beta polypeptides and their binding targets.
DERWENT CLASS: B04 D16
INVENTOR(S): GOEDDEL, D V; WORONICZ, J
PATENT ASSIGNEE(S): (TULA-N) TULARIK INC
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 5916760 | A | 19990629 | (199932)* | | 14 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 5916760 | A | Cont of | US 1997-887114 | 19970701 |
| | | Div ex | US 1997-890853 | 19970710 |
| | | | US 1998-99125 | 19980617 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| US 5916760 | A | Div ex | US 5851812 |

PRIORITY APPLN. INFO: US 1997-887114 19970701; US 1997-890853 19970710; US 1998-99125 19980617

AN 1999-384722 [32] WPIDS
CR 1999-080407 [07]; 1999-468406 [39]
AB US 5916760 A UPAB: 19990928
NOVELTY - A method (I) of screening for agents which modulate the interaction of human IKK- beta polypeptides and their binding targets, is new. IKK- beta is a novel IkB Kinase (I-Kappa B-Kinase, one of a family of inhibitory proteins which interact with Nuclear Factor Kappa B (NF-kB), see Finco et al., (1995)) which interacts with NIK (**Nuclear Factor-Kappa B-Inducing** Kinase).

DETAILED DESCRIPTION - A method (I) of screening for an agent which modulates the interaction of an IKK- beta polypeptide to a binding target, which comprises:

(i) incubating a mixture (A) under conditions in which, but for the presence of the agent, the polypeptide specifically binds the binding target at a reference affinity (rA) ((A) comprises:

(1) a polypeptide comprising at least 31 consecutive residues of a defined 756 residue amino acid sequence (X) given in the specification;

(2) a binding target of the polypeptide; and

(3) a candidate modulating agent); and

(ii) detecting the binding affinity of the polypeptide to the binding target to determine an agent-biased affinity (aA) (in which a difference

between aA and rA indicates that the agent modulates the binding of the polypeptide to the binding target).

USE - (I) may be used to screen for agents which modulate the interaction of IKK- beta polypeptides and their binding targets. Agents which modulate the IKK- beta binding are useful in a variety of diagnostic and therapeutic applications where the disease is associated with improper utilization of a pathway involving IKK- beta proteins (e.g. NF-kB activation and IKK- beta -dependent transcriptional activation). Example IKK- beta IkB Kinase inhibitors include known classes of serine/threonine Kinase (e.g. PKC (not defined)) inhibitors such as competitive inhibitors of ATP (adenine triphosphate) and substrate binding and antibiotics.
Dwg.0/0

L26 ANSWER 47 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-120207 [10] WPIDS
DOC. NO. NON-CPI: N1999-087749
TITLE: Method for storing ATM cells for data transmission mode switching - involves assigning FIFO's to store ATM cells of respective frames and assembling ATM cells into corresponding STM data frame.
DERWENT CLASS: W01
INVENTOR(S): LIEN, R L
PATENT ASSIGNEE(S): (LUCE) LUCENT TECHNOLOGIES INC
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 5859850 | A | 19990112 | (199910)* | | 8 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| US 5859850 | A | US 1995-579706 | 19951228 |

PRIORITY APPLN. INFO: US 1995-579706 19951228
AN 1999-120207 [10] WPIDS
AB US 5859850 A UPAB: 19990310
The method involves receiving multiple isochronous ATM composite cells from an ATM network. Each ATM cell is grouped into its respective original transmitted frame. The jitter and delay induced into the ATM cells by passage through ATM network is removed using FIFOs (510,510N). Each of **NFIFOs** is assigned to store the cells of its respective frame. The ATM cells are assembled into a corresponding STM data frame. The frame clock from the ATM cells are recovered.

ADVANTAGE - Determines beginning of each ATM cell and selects FIFO for storing new ATM cells without resorting to special cell headers, special makers, special VCIs etc. Determines to which 125 microseconds frame as ATM cell belongs and routes cell to FIFI regardless of cell arrival. Provides lowest possible queuing delay for any desired amount of jitter capability. Provides arbitrary amount of jitter delay. Stores data from asynchronous transmission mode system prior to or subsequent to switching by synchronous transmission mode switch.
Dwg.5/6

L26 ANSWER 48 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:195183 BIOSIS
DOCUMENT NUMBER: PREV199900195183
TITLE: The proto-oncogene Cot kinase participates in CD3/CD28 induction of NF-kappaB acting through the NF-kappaB-inducing kinase and IkappaB kinases.
AUTHOR(S): Lin, Xin; Cunningham, Emmett T., Jr.; Mu, Yajun; Geleziunas, Romas; Greene, Warner C. [Reprint author]
CORPORATE SOURCE: Departments of Medicine, Microbiology, and Immunology, Gladstone Institute of Virology and Immunology, University of California San Francisco, San Francisco, CA, 94141, USA
SOURCE: Immunity, (Feb., 1999) Vol. 10, No. 2, pp. 271-280. print. ISSN: 1074-7613.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 May 1999
Last Updated on STN: 25 May 1999

AB The proto-oncogene Cot/Tpl-2 **encodes** a MAP3K-related serine-threonine kinase. Expression of wild type Cot activates the IkappaB kinases (IKK) leading to induction of NF-kappaB. Conversely, expression of kinase-deficient Cot inhibits CD3/CD28 but not TNFalpha induction of NF-kappaB. These findings suggest the selective involvement of Cot/Tpl-2 or a closely related kinase in the CD3/CD28 costimulatory pathway leading to induced nuclear expression of NF-kappaB. In contrast, a kinase-deficient mutant of the NF-kappaB-inducing kinase (NIK) inhibits both CD3/CD28 and TNFalpha signaling, indicating that these pathways converge at or prior to the action of NIK. Consistent with such a sequential function of these two kinases, Cot physically assembles with and phosphorylates NIK in vivo.

L26 ANSWER 49 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:23363 BIOSIS
DOCUMENT NUMBER: PREV200400022995
TITLE: Alymphoplasia is caused by a point mutation in the mouse gene **encoding** Nf-kappab-inducing kinase.
AUTHOR(S): Shinkura, Reiko; Kitada, Kazuhiro; Matsuda, Fumihiko; Tashiro, Kei; Ikuta, Koichi; Suzuki, Misao; Kogishi, Katsumi; Serikawa, Tadao; Honjo, Tasuku [Reprint Author]
CORPORATE SOURCE: Department of Medical Chemistry, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto, 606-8501, Japan
honjo@mfour.med.kyoto-u.ac.jp
SOURCE: Nature Genetics, (July 1999) Vol. 22, No. 1, pp. 74-77. http://www.nature.com/ng/. online. ISSN: 1061-4036 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
OTHER SOURCE: DDBJ-AF143094; EMBL-AF143094; GenBank-AF143094
ENTRY DATE: Entered STN: 31 Dec 2003
Last Updated on STN: 31 Dec 2003

AB The alymphoplasia (aly) mutation of mouse is autosomal recessive and characterized by the systemic absence of lymph nodes (LN) and Peyer's patches (PP) and disorganized splenic and thymic structures with immunodeficiency. Although recent reports have shown that the interaction between lymphotoxin (LT) and the LT beta-receptor (Ltbetar, **encoded** by Ltbr) provides a critical signal for LN genesis in mice, the aly locus on chromosome 11 is distinct from those for LT and its receptor. We found that the aly allele carries a point mutation causing an amino acid substitution in the carboxy-terminal interaction domain of

Nf-kappab-inducing kinase (Nik, **encoded** by the gene Nik). Transgenic complementation with wild-type Nik restored the normal structures of LN, PP, spleen and thymus, and the normal immune response in aly/aly mice. In addition, the aly mutation in a kinase domain-truncated Nik abolished its dominant-negative effect on Nf-kappab activation induced by an excess of Ltbetar. Our observations agree with previous reports that Ltbetar-deficient mice showed defects in LN genesis and that Nik is a common mediator of Nf-kappab activation by the tumour necrosis factor (TNF) receptor family. Nik is able to interact with members of the TRAF family (Traf1, 2, 3, 5 and 6), suggesting it acts downstream of TRAF-associating receptor signalling pathways, including Tnfr, Cd40, Cd30 and Ltbetar. The phenotypes of aly/aly mice are more severe than those of Ltbr-/- mice, however, indicating involvement of Nik in signal transduction mediated by other receptors.

L26 ANSWER 50 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-044664 [04] WPIDS
CROSS REFERENCE: 1999-044580 [04]; 1999-094902 [08]
DOC. NO. CPI: C1999-013968
TITLE: New isolated peptide comprising a specified 947 amino acid sequence - has e.g. kinase activity, kinase inhibitory activity, IkB kinase-alpha binding activity, and IkB kinase-alpha binding inhibitory activity.
DERWENT CLASS: B04
INVENTOR(S): ROTHE, M; WU, L
PATENT ASSIGNEE(S): (TULA-N) TULARIK INC
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 5844073 | A | 19981201 | (199904)* | | 15 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 5844073 | A | Div ex | US 1997-887518 | 19970703 |
| | | | US 1998-23321 | 19980213 |

PRIORITY APPLN. INFO: US 1997-887518 19970703; US 1998-23321 19980213
AN 1999-044664 [04] WPIDS
CR 1999-044580 [04]; 1999-094902 [08]
AB US 5844073 A UPAB: 19990224
An isolated peptide (I) comprising a 947 amino acid sequence as given in the specification is new. Also claimed is an isolated polypeptide (II) comprising at least 10 consecutive amino acid residues of (I), including amino acid 25.

USE - (II) has one or more activities selected from kinase activity, kinase inhibitory activity, IkB kinase- alpha binding activity, IkB kinase- alpha binding inhibitory activity, IkB kinase-B binding activity, IkB kinase-B binding inhibitory activity, tumour necrosis factor receptor-associated factor 2 binding activity, tumour necrosis factor receptor-associated factor 2 binding inhibitory activity, IkB binding activity, IkB binding inhibitory activity, nuclear factor-kB activating activity and nuclear factor-kB inhibitory activity (all claimed). (I) and (II) may be used in diagnosis (e.g. genetic hybridisation screen for

**nuclear-factor-kB-inducing** kinase (NIK) transcripts), therapy (e.g. NIK kinase inhibitors to inhibit tumour necrosis factor (TNF) signal transduction), and in the biopharmaceutical industry (e.g. as immunogens, reagents for isolating other transcription regulators, and reagents for screening chemical libraries for lead pharmacological agents).
Dwg.0/0

L26 ANSWER 51 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-044580 [04] WPIDS
CROSS REFERENCE: 1999-044664 [04]; 1999-094902 [08]
DOC. NO. CPI: C1999-013892
TITLE: Probe, vector or recombinant nucleic acid **encoding** a polypeptide, especially human **nuclear factor kappa-B-inducing** kinase protein - useful for producing recombinant protein.
DERWENT CLASS: B04 D16
INVENTOR(S): ROTHE, M; WU, L
PATENT ASSIGNEE(S): (TULA-N) TULARIK INC
COUNTRY COUNT: 84
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 5843721 | A | 19981201 | (199904)* | | 15 |
| WO 9901471 | A1 | 19990114 | (199909) | EN | |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW | | | | | |
| W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW | | | | | |
| AU 9883820 | A | 19990125 | (199923) | | |
| EP 1012174 | A1 | 20000628 | (200035) | EN | |
| R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| AU 724178 | B | 20000914 | (200051) | | |
| JP 2001510348 | W | 20010731 | (200148) | | 34 |
| CA 2295999 | C | 20040427 | (200430) | EN | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| US 5843721 | A | US 1997-887518 | 19970703 |
| WO 9901471 | A1 | WO 1998-US13841 | 19980702 |
| AU 9883820 | A | AU 1998-83820 | 19980702 |
| EP 1012174 | A1 | EP 1998-934252 | 19980702 |
| | | WO 1998-US13841 | 19980702 |
| AU 724178 | B | AU 1998-83820 | 19980702 |
| JP 2001510348 | W | WO 1998-US13841 | 19980702 |
| | | JP 1999-507409 | 19980702 |
| CA 2295999 | C | CA 1998-2295999 | 19980702 |
| | | WO 1998-US13841 | 19980702 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|

| | | | |
|---|---|---|---|
| AU 9883820 | A | Based on | WO 9901471 |
| EP 1012174 | A1 | Based on | WO 9901471 |
| AU 724178 | B | Previous Publ. | AU 9883820 |
| | | Based on | WO 9901471 |
| JP 2001510348 | W | Based on | WO 9901471 |
| CA 2295999 | C | Based on | WO 9901471 |

PRIORITY APPLN. INFO: US 1997-887518 19970703
AN 1999-044580 [04] WPIDS
CR 1999-044664 [04]; 1999-094902 [08]
AB US 5843721 A UPAB: 20040511

A probe, vector or recombinant nucleic acid comprising a defined cDNA sequence of 3156 bp (I) given in the specification is new. Also claimed are: (1) a probe, vector or recombinant nucleic acid comprising at least 24 consecutive nucleotides of (I), including nucleotides 72-75; (2) a probe, vector or recombinant nucleic acid **encoding** a defined sequence of 947 amino acids (II) given in the specification; (3) a probe, vector or recombinant nucleic acid **encoding** a polypeptide comprising at least 10 consecutive amino acids of (II), including amino acid 25; (4) cells containing probes, vectors or recombinant nucleic acids as above.

USE - The probe, vector or recombinant nucleic acid is used for making recombinant polypeptides. The polypeptide having sequence (II) is an Ala25Pro variant of the human **nuclear factor kappa-B-inducing** kinase protein described in Nature, 385, 540 (1997). The polypeptide of (3) has one or more activities selected from kinase activity, kinase inhibitory activity, IkappaB kinase-alpha binding activity, IkappaB kinase- alpha binding inhibitory activity, tumour necrosis factor receptor-associated factor 2 binding activity, tumour necrosis factor receptor-associated factor 2 binding inhibitory activity, IkappaB binding activity, IkappaB binding inhibitory activity, nuclear factor-kappaB activating activity and nuclear factor-kappaB inhibitory activity.

Dwg.0/0

L26 ANSWER 52 OF 54 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-199868 [18] WPIDS
DOC. NO. NON-CPI: N1998-158919
TITLE: High frequency circuit for CT-2 digital cordless telephone system - establishes suitable spurious frequency for carrier wave signal, such that it is integral multiple of intermediate frequency.
DERWENT CLASS: W01 W02
PATENT ASSIGNEE(S): (SONY) SONY CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| JP 10051405 | A | 19980220 | (199818)* | | 8 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| JP 10051405 | A | JP 1996-206173 | 19960805 |

PRIORITY APPLN. INFO: JP 1996-206173 19960805

AN 1998-199868 [18] WPIDS
AB JP 10051405 A UPAB: 19980507
The circuit establishes the spurious frequency (FSP) for a carrier wave signal suitably such that it is an integral multiple of intermediate frequency (FiF) that is, **nFiF** where n is a positive integer. The spurious frequency is in the range of 862- 863.65MHz, with respect to the intermediate frequency.
ADVANTAGE - Enables satisfying spurious specification. Reduces power consumption.
Dwg.1/5

L26 ANSWER 53 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:138395 HCAPLUS
DOCUMENT NUMBER: 126:233796
TITLE: Dexamethasone attenuates NF-κB DNA binding activity without inducing IκB levels in rat brain in vivo
AUTHOR(S): Tino Unlap, M.; Jope, Richard S.
CORPORATE SOURCE: Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL, 35294-0017, USA
SOURCE: Molecular Brain Research (1997), 45(1), 83-89
CODEN: MBREE4; ISSN: 0169-328X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This investigation tested if glucocorticoid hormones modulate activation of the NF-κB transcription factor in rat brain in vivo. Dexamethasone (2 mg/kg) administration decreased NF-κB DNA binding in cerebral cortex and hippocampus nuclear exts., maximally at 3-6 h after dexamethasone, followed by recovery at 24 h. Dexamethasone did not inhibit NF-κB by increasing the level of the inhibitory protein IκBα, as occurs in some peripheral cells, but instead lowered IκBα levels. Direct protein-protein inhibition by glucocorticoids was indicated by co-precipitation of glucocorticoid receptors with the p65 NF-κB subunit. Thus, glucocorticoids inhibit NF-κB DNA binding in rat brain, apparently by complexing with NF-κB subunits, which may contribute to the detrimental effects of glucocorticoids on neuronal function associated with oxidative stress and excitotoxicity.

L26 ANSWER 54 OF 54 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:409474 BIOSIS
DOCUMENT NUMBER: PREV199598423774
TITLE: The inflammatory cytokine response to Chlamydia trachomatis infection is endotoxin mediated.
AUTHOR(S): Ingalls, Robin R.; Rice, Peter A.; Qureshi, Nilofer; Takayama, Kunt; Lin, Juey Shin; Golenbock, Douglas T. [Reprint author]
CORPORATE SOURCE: Maxwell Finland Lab. Infectious Diseases, 774 Albany St., Boston, MA 02188, USA
SOURCE: Infection and Immunity, (1995) Vol. 63, No. 8, pp. 3125-3130.
CODEN: INFIBR. ISSN: 0019-9567.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Sep 1995

Last Updated on STN: 27 Sep 1995

AB Chlamydia trachomatis is a major etiologic agent of sexually transmitted diseases. Although C. trachomatis is a gram-negative pathogen, chlamydial infections are not generally thought of as endotoxin-mediated diseases. A molecular characterization of the acute immune response to chlamydia, especially with regard to the role of its lipopolysaccharide (LPS), remains to be undertaken. We extracted 15 mg of LPS from 5 times 10-12 C. trachomatis elementary bodies (EB) for analysis of structure and biological activity. When methylated lipid A was subjected to high-pressure liquid chromatography followed by mass spectrometry, the majority of the lipid A was found to be pentaacyl. The endotoxin activities of whole C. trachomatis EB and purified LPS were characterized in comparison with whole Salmonella minnesota R595 and with S. minnesota R595 LPS and lipooligosaccharide from Neisseria gonorrhoeae. Both C. trachomatis LPS and whole EB induced the release of tumor necrosis factor alpha from whole blood ex vivo, and C. trachomatis LPS was capable of **inducing** the translocation of **nuclear factor KB** in a Chinese hamster ovary fibroblast cell line transfected with the LPS receptor CD14. In both assays, however, C. trachomatis was apprx 100-fold less potent than S. minnesota and N. gonorrhoeae. The observation that C. trachomatis is a weak inducer of the inflammatory cytokine response correlates with the clinical observation that, unlike N. gonorrhoeae infection, genital tract infection with C. trachomatis is often asymptomatic. The ability of specific LPS antagonists to completely inhibit the tumor necrosis factor alpha-inducing activity of whole C. trachomatis EB suggests that the inflammatory cytokine response to chlamydia infection may be mediated primarily through LPS. This implies that the role of other surface protein antigens, at least in terms of eliciting the proinflammatory cytokine response, is likely to be minor.